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CLINIC BUILDING
Erected 1921

CLEVELAND CLINIC HOSPITAL
Erected 1924

IN RETROSPECT

After the Armistice Dr. F. E. Bunts, Dr. George Crile, Sr., and Dr. W. E. Lower, who had been associated in private practice since the Nineties and also in Base Hospital 4 in World War I, resolved to initiate a group clinic in Cleveland. Dr. Bunts and Dr. Crile were general surgeons, and Dr. Lower was a urologist. To round out this group, Dr. John Phillips, an internist, was invited to join the undertaking. Accordingly on February 5, 1921, the Cleveland Clinic Foundation was incorporated with these four men as Founders, and on February 26, 1921, the Cleveland Clinic Building was formally opened.

The Founders surrounded themselves with a staff of promising young men, and the facilities provided attracted a continually increasing number of patients. The need for a hospital soon became obvious and even more acute in 1924 at the expiration of Dr. Crile's service as Visiting Surgeon to Lakeside Hospital. A new Hospital Building was opened in June, 1924, and an addition in 1929.

Space for research in biophysics was included in plans of the original Clinic Building. This space soon proved to be insufficient, and in 1928 a separate eight-story building was erected. In the Clinic disaster on May 15, 1929, Dr. John Phillips lost his life, and the Clinic Building was so badly damaged that immediate rehabilitation was impossible. A new Clinic Building was opened in September, 1931.

In 1941 the Museum of Power, Intelligence, and Personality, based on studies in physiology and comparative anatomy, made by Dr. Crile and his associates, was opened to the public. Except for this building no additions had been made for the preceding ten years.

Continued growth rendered the physical equipment inadequate to care for the augmented necessities, but the calamity of a second World War made it imperative to defer all expansion. Immediately after release of restriction upon building, work was begun. An addition to the Hospital is under way, to be followed by a similar increase in space for research, and erection of seven more stories to the Main Clinic Building. This will provide for more than 50 per cent increase in the work of the Clinic.

The Cleveland Clinic carries on in the spirit of its Founders who dedicated it to

> "Better care of the sick,
> Further study of their problems,
> More teaching of those who serve."

HOWARD DITTRICK, M.D.
Editorial Director.

THE TREATMENT OF PERNICIOUS ANEMIA

RUSSELL L. HADEN, M.D.

Pernicious anemia is a true deficiency disease for which specific replacement therapy is available. In idiopathic pernicious anemia the deficiency once present continues throughout the life of the patient. The disease is never "cured." The deficiency responsible for the symptoms is satisfied, however, by complete and continued treatment. A symptomatic deficiency in the specific factor may occur temporarily, as in pregnancy where the need is for a time greater than the supply, or when absorption is interfered with as in sprue or other abnormality of the small intestine. Here the deficiency disappears with the relief of the underlying causative disease, although specific therapy is usually helpful.

The seriousness of idiopathic pernicious anemia is best emphasized by the fact that it was always fatal before the introduction of liver treatment by Minot and Murphy in 1926 and is still fatal without specific therapy. While anemia is always present and is usually the early symptom, neurologic involvement occurs almost always in time in untreated cases and usually in patients not completely treated. Subacute combined sclerosis of the spinal cord may lead to a crippling and permanent disability. A disease which is always fatal if untreated and often leads to serious permanent disability if insufficiently treated merits serious attention.

The first consideration is a correct diagnosis. If it is definitely determined that the patient has idiopathic pernicious anemia, treatment is necessary throughout life. All too often a patient is given liver extract for an anemia which has not been properly studied, and a definite diagnosis of pernicious anemia made. The patient improves but does not continue treatment because he does not understand that this is required permanently. Later a spinal cord lesion develops due to discontinuing the treatment; or it may not be realized by the physician that treatment must completely satisfy the deficiency to prevent progress in the neurologic involvement characteristic of the disease. If the anemia is not pernicious anemia, liver extract is seldom needed.

Pernicious anemia is a disease of older people. In 406 cases studied at the Cleveland Clinic only 5 were less than 30 years of age. In a total number of 558 I have observed the disease begin under 20 years of age in only one individual. The disease was first observed over 60 years of age in 41.7 per cent. One patient was 88 years old when first diagnosed. Fifty-two per cent were in the 40 to 60 group.

Three characteristic aspects or phases are observed in pernicious anemia: (1) gastro-intestinal, (2) hematologic, and (3) neurologic. The specific factor concerned is formed in the stomach by interaction of a ferment or other substance (intrinsic factor) secreted by the gastric glands on some element of ingested food (extrinsic factor). The substance formed by the interaction of intrinsic and extrinsic factors is absorbed from the gastro-intestinal tract. It is necessary for (1) normal gastro-intestinal function, (2) the normal growth and development of red blood cells, and (3) the normal nutrition of the nervous system. There should be an excess of the specific factor which is stored in the liver after absorption from the small intestine. This represents an overflow after the current needs of the body are satisfied and is stored to supply added demands.

No patient with idiopathic pernicious anemia has free hydrochloric acid in the stomach. The achlorhydria seems to precede the anemia and other symptoms of the disease by many years. It probably is congenital in most cases. The mucous membrane of the stomach is atrophic on gastroscopic examination. The papillae of the tongue are atrophic also. A coated tongue in active, untreated pernicious anemia is rarely seen. The surface is almost always clean, giving the tongue a "bald" appearance. The patient often complains of a sore tongue. This was a primary complaint in over 10 per cent of our series. Partly as a result of the absence of hydrochloric acid and probably partly as a result of a lack of nutritional factors, diarrhea is common. Many other gastro-intestinal symptoms are complained of, such as "indigestion", anorexia, nausea, vomiting, excessive gas formation, and jaundice. As a result of the gastro-intestinal disturbances most patients lose weight. With specific therapy the glossitis disappears, the papillae become normal and the tongue may become coated. Other gastro-intestinal symptoms usually clear up. The achlorhydria is permanent.

The blood findings are characteristic. The typical patient has a marked anemia with large red cells filled with hemoglobin (macrocytic and hyperchromic anemia). The mean volume of the erythrocyte is increased, so the volume index is high. Since there is no disturbance in hemoglobin formation, the stroma is filled with hemoglobin. The cells are larger than normal, so the mean cell hemoglobin content is increased and the color index is high. In 558 patients studied for red cell changes all have shown a macrocytosis if untreated. Often the volume index is high when the color index is normal or less than 1. The cell-size is by far the best diagnostic indicator of pernicious anemia and is the most important criterion of complete therapy.

The achlorhydria and the macrocytosis of the red cells are the two constant findings in untreated pernicious anemia. An anemic patient with large red cells (increased volume index) and achlorhydria almost without exception is suffering from pernicious anemia.

The bone marrow reflects the effects of a deficient supply of the erythrocyte-maturing factor. The first change is slowing of the rate of release of red cells. The cells released are larger than normal since maturation is not complete. This increase in the size of the cell is the first and most sensitive indicator of a deficient supply of the specific factor responsible for pernicious anemia. The immature erythrocytes remain longer and crowd the marrow so the marrow becomes red due to filling with cells which normally would be delivered into the circulation. As the deficiency progresses such cells as do reach the blood stream are of many sizes and shapes and some are nucleated. Many cells die in the marrow. The end product of hemoglobin destruction is bilirubin. The increased amount of the bile pigment may exceed the capacity of the liver to excrete it, so definite clinical jaundice may develop. It was once thought that the finding of megaloblasts in the blood film was the best diagnostic criterion of pernicious anemia. The appearance of microcytes, poikilocytes, nucleated red cells and basophilia is a late development in pernicious anemia. The one constant and characteristic early sign is the macrocytosis, and the hematologic diagnosis of pernicious anemia should be based on this finding. The reticulocyte count is low in pernicious anemia. When specific liver therapy is given, the reticulocyte count rapidly rises to a peak since the immature, unfinished red cells are now completed and delivered into the circulation. The height of the reticulocyte curve rises with the degree of hyperplasia and immaturity of the marrow. The redder the marrow the more severe the disease and the higher the reticulocyte count on treatment since there are larger numbers of immature cells to be released.

The leucocyte count is seldom above normal in pernicious anemia. The leucocytes in the circulation are often larger than normal and usually well lobulated. The hyperplasia of the erythroblastic tissues in the marrow seemingly interferes with the normal growth of granulocytes by crowding out the leucoblastic tissues. The granulocytes remain longer than normal in the marrow so when released show hypersegmentation of the nucleus indicating they are older than the average granular or white cell. The platelets are often decreased, probably for the same reason.

To summarize the blood findings in pernicious anemia: The first change is an increase in volume (macrocytosis) of the red cells and an anemia due to slowing of rate of release of the red cells into the blood

stream. As the disease progresses the anemia becomes more marked, the macrocytosis persists, and more immature cells—poikilocytes, megaloblasts, and normoblasts—appear. The reticulocyte count is low. The bone marrow is hyperplastic and red. The leucocyte count is below normal and the white cells in the circulation tend to show increased lobulation. With adequate specific therapy the reticulocyte count rises sharply showing that the erythrocytes are being matured in the marrow. With complete treatment the blood returns to normal and remains so. The one constant abnormality when the disease is active is the macrocytosis of the red cells. It is the earliest variation from normal to appear and the last to disappear and is the best indicator of pernicious anemia from the blood standpoint. It is by far the best criterion of the completeness of treatment. All untreated patients in our series of 578 patients with pernicious anemia have had a macrocytic anemia, and often only the macrocytosis. All correctly and completely treated patients show no macrocytosis.

The neurologic lesions are both peripheral and central. There is probably always some degree of neuritis, usually some degeneration of the tracts of the spinal cord, and at times cerebral symptoms due to involvement of the brain. It seems proved that the neurologic lesions are due to a deficiency in the nutrition of the nervous system. It is likely that the same nutritional factor necessary for the maturation of the red cells is required for the nervous system also. It is possible that other substances are involved, but it is known that the deficiency responsible for the neurologic lesions is satisfied by the use of liver and liver substitutes regardless of whether it is dependent on the same factor or some related or independent factor.

The neurologic involvement is manifested by paresthesia of the hands and feet, in-co-ordination or spasticity. The most common finding on examination is a loss of vibratory sense in the lower extremities. Abnormalities in the reflexes and position sense are often present. In 325 patients on whom the vibration sense was tested this was found abnormal (lost or diminished) in 245 or 72.3 per cent. Nearly half (45.8 per cent) of the entire group of 406 patients complained on admission of numbness and tingling in the extremities. Over 10 per cent already had a spinal cord lesion making walking difficult due to in-co-ordination or spasticity. A true psychosis was observed in only one patient.

In treating pernicious anemia the object is to satisfy completely and permanently the deficiency responsible for the disease. Whole liver by mouth, oral stomach extracts, and oral and parenteral liver extracts are available forms of specific treatment. While it is an excellent idea for patients to eat liver as a part of the diet, it is difficult to treat satis-

factorily pernicious anemia by eating liver. Stomach extracts can be given by mouth only. Liver extract given intramuscularly is thirty times as active as the same amount taken by mouth. By far the best method of treatment is the intramuscular or subcutaneous use of a potent liver extract. Some extracts can be given intravenously, but the intravenous method has no advantages over subcutaneous or intramuscular administration. It is probable that a patient is more apt to become sensitive to the extract if given intravenously. There are many different liver extracts on the market varying greatly in strength. The strongest extract contains at least 15 units per cc., a unit being the amount of specific principle theoretically required to supply the amount of specific factor needed for a day. There is no exact method for assaying liver extracts. Many extracts labeled 15 units may contain many more. The same manufacturer may offer numerous extracts varying only in potency, which is confusing. I see no point in treating most patients suffering from pernicious anemia with other than a concentrated extract (15 units per cc.).

Since extracts of different manufacturers may vary, it is wise to select one good extract and use this with all patients. Where the neurologic involvement is serious, some clinicians have thought that a less concentrated extract might contain some substance which is not present in the concentrated extract and which is an aid in relieving the disease of the nervous system. This view is debatable.

Having selected a potent concentrated extract the method of administration must be decided upon. Many different ways have been advised. The whole subject is much colored by personal opinion. I believe strongly that the most satisfactory method is intensive therapy at the beginning of treatment. Certainly in some cases less intensive treatment might be equally as good. There is no way to gauge from the standpoint of the patient the amount of specific factor needed by any individual. The material is not expensive and the results of inadequate treatment are so serious it seems sensible to administer the liver extract in amounts which would cover the needs of all patients. After the initial period of intensive therapy the injections need not be given so often.

The method found uniformly satisfactory is the following schedule:

First two weeks daily injections of 1 cc. of a potent extract containing 15 units per cc.

Next three-month period twice weekly injections of 1 cc. of the same extract.

Next three-month period weekly injections of 1 cc. of the same extract.

Remainder of the patient's life monthly injections of 1 cc. of the same extract.

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This plan of treatment has been followed for the past fifteen years. With it the blood is always returned to normal and maintained if the diagnosis is correct. The neurologic lesions never advance and usually improve often to a striking degree; the gastro-intestinal symptoms are relieved entirely although the achlorhydria is uninfluenced.

With adequate treatment the patient in four or five days notices an improvement in the appetite and develops a sense of well being. The weight soon begins to increase; a sore tongue disappears and gastro-intestinal symptoms clear up. This clinical improvement is paralleled by a steady rise in the red cells and hemoglobin and an outpouring of young cells (reticulocytes). Soon the reticulocyte count falls to normal (less than 1 per cent) but the change in the blood continues until the red cell count and hemoglobin are normal and the red cell size is normal as shown by a volume index of 1 or less. The papillae of the tongue return entirely to normal.

By far the best indicator of the adequacy of treatment is the erythrocyte size. If the volume index does not return to normal and remain normal, the treatment is not complete. A patient should always have a careful blood study at three or six-month intervals to measure the results of treatment. If the red cell count remains five million or over, one can also be sure that treatment is adequate. It is best, however, to do a volume index or other test to determine cell size as even a slight increase in size is a warning that more treatment is needed.

The neurologic signs and symptoms are the hardest to influence and improve much more slowly than the anemia. If progress is not satisfactory, injections should continue to be given at weekly intervals indefinitely. The lack of improvement neurologically may be due to permanent damage to the nerve tract which cannot be altered. So often this damage takes place while the patient is receiving treatment but inadequate treatment. It is remarkable how striking the improvement in a neurologic lesion can be when properly treated. A patient may be completely crippled due to an extensive cord lesion and still regain use of the legs and walk satisfactorily. Seldom is the vibratory sense completely regained—some parasthesia is apt to persist. A neurologic lesion should never develop or progress in an adequately treated patient.

The treatment of any deficiency disease is influenced by certain intercurrent diseases, especially infections. More extract should be given if such occur.

One troublesome complication of liver therapy is the development of allergic reactions, principally hives, following the injection of liver extract. Most extracts are made from hog liver. Others are made from beef, horse, and sheep products. If difficulty is experienced, different ex-

tracts should be tried. So far I have not seen a patient who could not take some potent extract. Mild reactions may be controlled by giving small doses of adrenalin with the liver extract.

Iron is seldom required unless needed for some reason such as blood loss, apart from the pernicious anemia.

It is doubtful if added vitamins influence the neurologic lesions if liver therapy is given properly and intensively and an adequate diet is eaten. Hydrochloric acid is seldom needed.

SUMMARY

1. Pernicious anemia is a disease characterized by (a) macrocytic anemia with (b) achlorhydria, an atrophy of the papillae of the tongue and other gastro-intestinal symptoms, and (c) frequent neurologic signs and symptoms manifested by numbness and tingling of the extremities, lost vibratory sense, and disturbances in gait due to combined sclerosis of the spinal cord.

2. In a series of 406 consecutive patients with pernicious anemia (a) free hydrochloric acid was found in the gastric contents in only 1 patient, (b) all untreated patients had a macrocytic anemia, (c) the tongue was clean or atrophic in most patients, (d) nearly half complained of parasthesia or difficulty in walking, and (e) in three-fourths the vibratory sense was absent.

3. All symptoms and signs except the achlorhydria are due to a lack of some specific substance normally formed by the interaction of a ferment secreted by the stomach on some constituent of the ingested food and stored in the liver.

4. The deficiency in idiopathic pernicious anemia is permanent, so treatment is required throughout the life of the patient. The object of treatment is to satisfy completely the need for the lacking substance.

5. A satisfactory method of giving liver extract has been outlined.

6. Iron, hydrochloric acid, and other medication is seldom needed. A complete diet should be insisted upon.

7. With adequate therapy (a) the blood returns to normal and remains so, (b) the tongue becomes normal and other gastro-intestinal symptoms such as indigestion and diarrhea disappear, (c) the neurologic symptoms improve or even clear completely, and (d) the achlorhydria is permanent.

8. In pernicious anemia (a) the seriousness of the disease must be appreciated, (b) the disease must be correctly diagnosed, and (c) treatment must be complete and permanent.

PRESENT STATUS OF THE SURGICAL TREATMENT OF HYPERTHYROIDISM

GEORGE CRILE, JR., M.D., AND ROBERT S. DINSMORE, M.D.

The surgical conquest of hyperthyroidism, initiated at the turn of the century and established in safety by the preoperative use of iodine, had become so well accepted that until the introduction of thiouracil, few chose to consider hyperthyroidism anything other than a surgical problem. Today, as a result of the discovery of powerful and effective drugs, the controversial issue of whether hyperthyroidism is better treated by conservative (medical) management has again arisen.

Even before the introduction of thiouracil the mortality rate of hyperthyroidism treated by experienced surgeons was less than 1 per cent. Improvement in anesthesia, in surgical technic, in preoperative and postoperative care, and a keener appreciation of the factors that increase the risk of operation contributed materially to this advance. Since at the present time the safety of thyroidectomy performed by a competent surgeon is about the same as that of thiouracil therapy, the decision as to which is the treatment of choice must be decided on the basis of end results and morbidity.

When hyperthyroidism arises as the result of functional activity in a long-standing adenoma, it is not surprising that removal of the benign tumor which is responsible for the hyperthyroidism is followed by cure of the disease and an almost negligible incidence of recurrent hyperthyroidism. The factors responsible for the development of the original adenoma may no longer be in operation, and if excision has been complete, there is no reason for the hyperthyroidism to recur.

In diffuse goiter with hyperthyroidism, however, the entire gland is stimulated to hypertrophy, hyperplasia, and hyperfunction by causes which are not fully understood. It seems unlikely that the primary seat of the disease is in the thyroid gland itself. Subtotal thyroidectomy, moreover, does nothing to eliminate the factors that originally stimulated the hyperplasia and hyperfunction. Hence, the surprising clinical feature is not that hyperthyroidism occasionally recurs, but rather that the disease does not *always* recur.

The incidence of persistent hyperthyroidism following operation is easy to determine. Persistence of the hyperthyroidism represents a technical error resulting from insufficient removal of thyroid tissue. This accident is rare and occurs only in a fraction of 1 per cent of all cases of hyperthyroidism if thyroidectomy has been well done. The true incidence of recurrent hyperthyroidism, on the other hand, is most difficult

to determine and will depend almost entirely on the length of the follow up. Although the greatest incidence of recurrent hyperthyroidism is in the first two years following thyroidectomy, it may occur at any time. A patient may remain well for twenty years only to develop, late in life, recurrent hyperthyroidism. It is estimated that the over-all incidence of persistent and recurrent hyperthyroidism does not exceed 5 per cent.

If these figures are further broken down to separate the diffuse goiters with hyperthyroidism (true Graves' disease) from the nodular goiters with hyperthyroidism, it is apparent that the vast majority of patients with recurrent hyperthyroidism are those who had diffuse hyperplastic goiters. It is the true exophthalmic goiter that has the highest tendency to cause recurrent hyperthyroidism after thyroidectomy.

Total thyroidectomies are seldom performed in the treatment of hyperthyroidism because of the prohibitive incidence of parathyroid tetany. Studies conducted in relation to total thyroidectomy for heart disease and experiments on animals have shown that unless every vestige of thyroid tissue is removed, regeneration of the thyroid promptly restores its function to normal. This regeneration occurs as a compensatory hypertrophy and hyperplasia stimulated by the pituitary gland in response to a deficiency in circulating thyroid hormone. Since (1) the normal thyroid is capable of regeneration, (2) a considerable portion of the thyroid is left following subtotal thyroidectomy, and (3) the true causes of hypertrophy, hyperplasia, and hyperfunction of the thyroid in hyperthyroidism are not removed by thyroidectomy, why is it that the remnants of the thyroid do not always enlarge and cause a recurrence of the disease?

On the basis of present knowledge there is no answer to this question unless it is assumed that surgery merely breaks a link in a "vicious circle" of nervous and/or endocrine disorders. It is possible that subtotal thyroidectomy, by accomplishing a reduction to or below normal in the output of thyroid hormone, secondarily causes a subsidence of the factors that incited the thyroid gland to hyperfunction. The fact that recurrent hyperthyroidism and postoperative hypothyroidism are most commonly seen after operations for diffuse goiter with hyperthyroidism, and are seldom seen following operations for nodular goiter, is further evidence that some factor other than the amount of thyroid tissue left is responsible for the unpredictable occurrence of postoperative hypothyroidism and recurrent hyperthyroidism. If enough tissue is removed to induce a remission of the symptoms of Graves' disease, it is impossible to predict whether this interruption of the "vicious circle" will produce myxedema, will stabilize the function of the thyroid at a normal level, or will act but temporarily until the gland is again stimulated, and the

disease recurs. It is clear, therefore, that surgical treatment of diffuse goiter with hyperthyroidism is empiric in approach, unpredictable in outcome, and unphysiologic in principle, but from a clinical standpoint is safe, simple, and satisfactory.

Following subtotal thyroidectomy the mechanism of compensatory hypertrophy and hyperplasia and the factors which caused the original hyperfunction of the thyroid would be expected to continue to operate and to produce a recurrence of the goiter and of the hyperthyroidism. Yet this occurs in only a small percentage of cases. An unphysiologic procedure is proved empirically to be a sound clinical treatment. Is the treatment of hyperthyroidism with thiouracil safer, more predictable in its end results or more physiologic than removal of the gland?

So far as has been determined, the effect of thiouracil is primarily on the thyroid gland. By blocking formation of active thyroid hormone *thiouracil accomplishes a physiologic instead of an anatomic subtotal thyroidectomy*. If given in large enough doses over a long enough period of time it might often produce the physiologic equivalent of a *total* thyroidectomy.

The same questions can be asked about the results obtained with thiouracil as were asked about those following thyroidectomy. Why does not the thyroid in humans invariably enlarge rapidly as it does in animals? The pituitary gland is stimulated by the deficiency of thyroid hormone to pour out its thyroid-stimulating hormone. Hyperplasia of the thyroid results, but the enlargement of the gland usually is negligible. Occasionally there is a case in which the thyroid grows with incredible rapidity to enormous size,[1] but these cases are the exception and not the rule.

Why does not the hyperthyroidism invariably recur after withdrawal of the drug? Thiouracil, so far as is known, has no effect on the master system that first stimulated the thyroid gland. Prolonged remissions from hyperthyroidism, nevertheless, are obtained following thiouracil therapy in perhaps 50 per cent of the patients who receive adequate treatment. How long these remissions will last is uncertain. It would appear that physiologic thyroidectomy by thiouracil therapy breaks the "vicious circle" just as anatomic thyroidectomy does. When a remission is obtained with thiouracil the end results are unpredictable, just as they are following thyroidectomy. Recurrence of hyperthyroidism, however, is more common after a course of thiouracil than following an adequate thyroidectomy.

When severe postoperative hypothyroidism or myxedema occurs, the subsequent development of recurrent hyperthyroidism is extremely rare. Is this because the "vicious circle" is more completely broken by the

induction of severe hypothyroidism? I am convinced that it is not always because an excessive amount of thyroid tissue has been removed and that it is not because there is insufficient thyroid tissue left to regenerate and cause a recurrence if the stimulating mechanism were in operation. If thiouracil were less toxic and large doses could be given safely over a long period of time to produce a true myxedema and to maintain it for several months, the "vicious circle" might be so completely interrupted that recurrences would be rare.

Subtotal thyroidectomy and thiouracil therapy accomplish essentially the same end by different means. Both methods of treatment depend upon inducing a temporary remission of the hyperthyroidism. During this remission the "vicious circle" of the pathologic physiology is broken, and in those patients who are to remain well the abnormal stimulation of the thyroid is abolished.

Any drug which is as safe as a surgical operation and which can accomplish the same ends without incurring discomfort and occasional morbidity is a better therapeutic measure than surgery. Thiouracil has nearly but not quite fulfilled these qualifications. The risk of fatal agranulocytosis following its use is approximately the same as the risk of thyroidectomy for hyperthyroidism before thiouracil was known. But the risk of thyroidectomy for hyperthyroidism has been enormously reduced by the availability of thiouracil for preparation of the bad risk cases. Today, the risk of thyroidectomy for hyperthyroidism should be the risk of operating on a simple goiter. In the past the majority of deaths following thyroidectomy were in 3 groups, (1) hyperthyroidism in the aged, (2) hyperthyroidism complicated by organic heart disease, and (3) severe hyperthyroidism with basal metabolic rates above +75 per cent. Today hyperthyroidism in the aged and in those with serious heart disease can be controlled by thiouracil, without the risk of surgery. The surgeon is no longer faced with the decision as to whether he must risk a high mortality to effect a cure or see his patient slowly expire under palliative therapy. Medical management in these problems is clearly preferable to surgery.

Nor is there often cause to lose a patient from thyroid crisis no matter how severe the hyperthyroidism. Although routine preparation of all patients with thiouracil would entail a risk nearly equivalent to the sum of the two risks, it would be equally unwise to disregard the advantages of thiouracil preparation for a patient with severe hyperthyroidism. Such cases constitute perhaps only 3 per cent of all cases of hyperthyroidism, but it is in this group as well as in the aged and in hyperthyroidism associated with other diseases that the mortality of thyroidectomy occurs.

It is necessary, therefore, to revise established opinions of the safety of thyroidectomy for hyperthyroidism. We are accustomed to estimate the risks of thyroidectomy for hyperthyroidism as approximately 0.5 per cent. But with modern methods of preparation 734 consecutive thyroidectomies have been performed at the Cleveland Clinic without a death. Nearly half of these patients had hyperthyroidism. The surgical mortality of thyroidectomy for hyperthyroidism has thus become extremely low and should be comparable to that of operations for simple goiter—a small fraction of 1 per cent. With penicillin to control pneumonia and infection it is hard to see why mortality following thyroidectomy should occur as a result of anything other than embolic phenomena and unpredictable accidents.

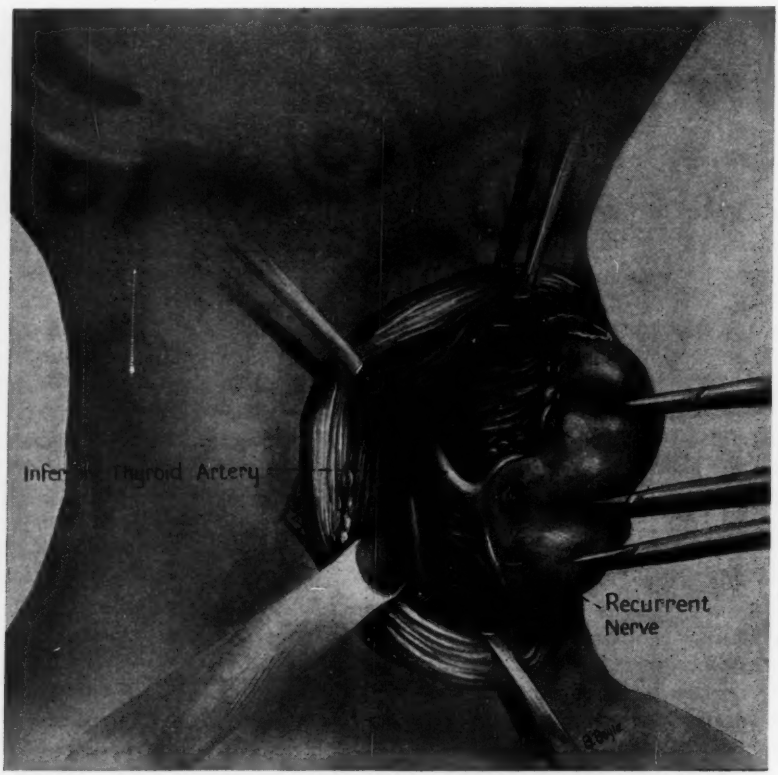

FIG.—Site of ligation of inferior thyroid artery.

The morbidity of thyroidectomy is still a consideration worthy of discussion. Again, the majority of technical accidents that occur are in a specific group of cases—thyroiditis, recurrent hyperthyroidism, and carcinoma. If these cases were eliminated, the treatment of primary hyperthyroidism by thyroidectomy would have an even smaller morbidity. For example, in a consecutive series of 400 cases, including recurrent goiters, thyroiditis, and carcinomas, there have been only 3 permanent recurrent nerve palsies. Two of these resulted from carcinomas in which the recurrent nerve was visualized and purposefully sacrificed in order to facilitate complete removal of the tumor. The third was a unilateral persistent paralysis occurring unaccountably in the course of an easy thyroidectomy. Laryngeal examination was made on all cases. The incidence of accidental injury to the recurrent nerve in this group is thus 0.25 per cent.

The adoption of a technic in which the inferior thyroid artery is ligated extracapsularly at the point where it passes behind the carotid (fig.) has been helpful in reducing the incidence of injuries to the recurrent nerve.* This procedure coupled with a more complete division of the superior pole and complete rotation of the thyroid gland from its bed has resulted in a better exposure of the vulnerable posterolateral surface of the gland, improved hemostasis, and in much greater facility in the handling of the friable vascular glands of patients who have been prepared for operation with thiouracil. Extracapsular ligation of the inferior thyroid vessel has not increased the small fraction of 1 per cent which constitutes the incidence of parathyroid tetany.

Since the mortality and morbidity of thyroid surgery are now so low, it is not surprising that the dangers of thiouracil have prevented its wide acceptance for use in the average case of hyperthyroidism. With the advent of newer, more powerful, and probably less toxic drugs, such as propyl thiouracil, now under trial, this attitude may change. There is always the danger that continued use of the drug may over a period of years result in gradual development of adenomas, as is seen in animals,[3] but as yet this tendency has not been apparent. In any case it is to be hoped that a drug will be found which will safely and completely break the "vicious circle" of thyroid stimulation and produce a lasting remission after its withdrawal. When this drug is discovered a means will have been found to replace anatomic thyroidectomy by physiologic thyroidectomy, and it can be hoped the remissions so induced will be as permanent and as satisfactory as are obtained by our present methods of treatment. The low toxicity of propyl thiouracil suggests that this

* No claim to originality in the development of this technic is made. Extracapsular ligation of the inferior thyroid artery is as old as surgery of the thyroid.

drug or a similar thiouracil derivative may be the ultimate answer to the problem of the small diffuse goiter with hyperthyroidism.

SUMMARY

1. The development of the anti-thyroid drugs has obviated the necessity of performing thyroidectomy on bad-risk patients at least until the hyperthyroidism is completely controlled.

2. If the bad-risk patients are treated or prepared for operation by thiouracil, the mortality following thyroidectomy performed on the remaining (good-risk) patients is less than that of treatment with thiouracil.

3. The morbidity (injury of recurrent laryngeal nerves, tetany, etc.) associated with thyroidectomy is less than 1 per cent.

4. In view of the low mortality and morbidity of thyroidectomy thiouracil is not recommended for routine treatment or preparation for operation and its use is reserved for those cases presenting unusual risks.

5. Thiouracil accomplishes a physiologic rather than an anatomic thyroidectomy and the mechanism by which it produces a remission is comparable in many respects to that of thyroidectomy.

6. It is hoped that some of the newer anti-thyroid drugs (propyl thiouracil, etc.) now under trial will prove to be non-toxic and will afford a means of effectively controlling hyperthyroidism without recourse to thyroidectomy.

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PRESENT STATUS OF THIOURACIL*

E. PERRY McCULLAGH, M.D.

It is now four years since Kennedy and Purves reported the effects of feeding Brassica seed diets to rats,[1] the goitrogenic effects of which were later shown to be due to their content of allyl thiourea. Their early studies showed that this goiter-producing effect was absent in hypophysectomized animals.[2] Since that time the work of the Mackenzies[3] and Astwood[4] has been followed by a flood of experimental and clinical literature on the subject.

* Presented in part as a lecture at the Post-graduate Course under the Auspices of the American College of Physicians, Chicago, November, 1945.

PHYSIOLOGIC EFFECTS

Thiourea has been shown to produce cretinism in rats[5] and to retard metamorphosis in tadpoles.[6] Enlargement of the thyroid occurs in rats in a few days on thiouracil feeding and recedes rapidly when feeding is stopped.[7] Such glands become highly vascular, with tall columnar cells lining their acini and with a marked decrease in colloid. In the pituitary gland thiourea causes a decrease in the number of acidophile cells and an increase in the basophiles, some of which are vacuolated. All of these changes apparently are due to a disappearance of thyroid hormone, since they can be prevented by giving thyroxin.[3]

Astwood found an almost complete disappearance of iodine from the thyroid gland of thiouracil-fed rats as early as five days,[7] and Larson showed that the thyroid glands of thiouracil-fed chicks[8] fail to take up radioactive iodine as well as do normal glands. The adrenal cortex atrophies under the effect of thiouracil,[9] and the plasma proteins change with an increase in β globulin, as after thyroidectomy.[10]

The mechanism by which these actions take place is thought to result from interference with certain enzyme systems necessary for the normal conversion of diiodotyrosine to thyroxin, since thiouracil tends to reduce the action of peroxidase[11] and tyrosinase.[12]

In the human, according to Williams,[11] absorption of thiouracil is very rapid and occurs chiefly from the stomach and duodenum. It is distributed rapidly throughout the body and can be demonstrated in high concentration in the pituitary, thyroid, and adrenal glands, and bone marrow. The white blood cells show a relatively greater concentration than the red cells.

None of the material is excreted in the stool, and about one-third may be excreted in the urine at ordinary dosage levels. The remainder presumably is changed in the body, probably in the liver.

The chief features of the physiologic action of the drug are summarized by Astwood:[13] "Shortly after the drug is administered the organism becomes unable to synthesize thyroid hormone at a normal rate, and the quantity of circulating hormone tends to fall. In response to this deficit an excess of thyrotropin is produced by the pituitary, which stimulates the thyroid to hyperplasia and to the release of the normal thyroid hormone stores therein. Within forty-eight hours of the first administration of the drug these compensatory changes are histologically visible, and for a number of days this mechanism is adequate to maintain the metabolic rate at a normal level. Eventually, however, the store of normal thyroid hormone is exhausted, as evidenced by a complete loss of demonstrable colloid at the end of seven to ten days, and as new

hormone can be made only at a reduced rate, the metabolic rate falls even though thyroid hyperplasia is still advancing."

THIOURACIL IN HYPERTHYROIDISM

In human hyperthyroidism the use of thiouracil produces a similar sequence of events. The thyroid gland becomes more vascular and hyperplastic and tends to enlarge. The rate of production of thyroid hormone diminishes, and as the stores are depleted the metabolic rate falls. Signs of hyperthyroidism disappear together with amelioration of associated conditions such as fibrillation or diabetes, which may have been caused or aggravated by the excess of thyroid hormone. If the drug is continued, myxedema may supervene. Rawson *et al.*[14] showed that in Graves' disease the thyroid gland treated with thiouracil had a decreased ability to retain iodine and that thyroglobulin prepared from such glands had a decreased physiologic activity when fed to myxedematous patients.

In a fairly large percentage of cases, some toxic effects are evident, the frequency depending to some extent on the dose used.

It is almost certain that over 6000 cases have been treated with thiouracil. My own experience covers 106 patients, almost entirely representing poor risk cases or instances of recurrence of hyperthyroidism after surgery.

THE DOSE

Early in the use of thiouracil the tendency was to use doses as large as 1.0 Gm. per day; more recently workers begin with doses not exceeding 0.6 Gm. and often 0.4 Gm. per day. We have adopted the plan of beginning with 0.6 Gm. per day in severe cases and 0.4 Gm. per day in those less severe. In all instances an attempt is made to reduce the dose to 0.4 Gm. per day or less as soon as definite clinical improvement occurs; when the metabolic rate approaches +15 per cent, we attempt to reduce the dose to 0.3 Gm. per day or less. We have not tried as a rule to discontinue the drug unless the metabolic rate has been maintained at normal range for at least two months. Blood counts are done twice weekly in cases showing any tendency to fall in level of white cells, and in all instances weekly blood counts are continued for at least fourteen weeks, then at less frequent intervals if the dose of thiouracil is reduced. At first the patient is seen weekly and later every two or three weeks. The metabolic rate is usually determined at intervals of two to three weeks until control is established, after which it is tested at less frequent intervals. The danger of agranulocytopenia from this drug is such that

we believe it should not be given except in cases where the blood count can be followed frequently.

RESPONSE TO THERAPY

The response to therapy in patients in whom there are no complications, in whom the goiter is not large, and in whom iodine has not been used for more than four weeks, is roughly predictable in most cases but varies widely in a few. The average fall of metabolic rate is about 1 per cent per day. Many cases, however, respond much more slowly. Chart 1 represents a group of patients with moderate hyperthyroidism. The first B.M.R. charted was taken before treatment in each case. The second B.M.R. is the one which first became normal or one representing the first level determined after twelve weeks of therapy. One patient previously untreated failed to show any response until after the dose was increased to 1.4 Gm. per day in the fourth month of treatment. She was

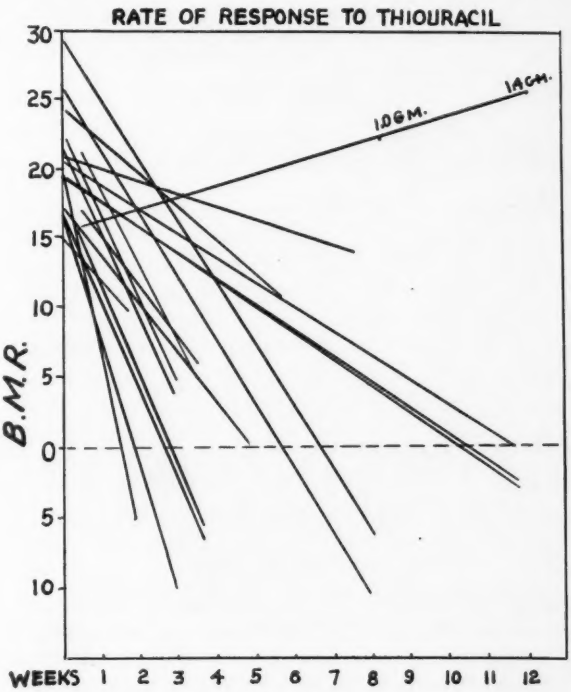

Chart 1

33 years of age and had a hyperplastic goiter of moderate size. In more severe cases (chart 2) the response is slower and varies greatly, and in a few, considerable resistance to treatment may be present for many months (chart 3). Such resistance is demonstrated by a woman, aged 55, now under observation. Thiouracil was begun in April, 1944. The metabolic rate decreased from +68 to +8 in four months but rose promptly when the thiouracil dose was reduced to 0.2 Gm. per day. Thyroid lobectomy was performed after one year of treatment. Lugol's solution 1 cc. 3 times per day was given for six weeks preceding operation. Later, following four months of thiouracil therapy, the metabolic rate was not less than +24 per cent in spite of doses of thiouracil as high as 1.2 Gm. per day.

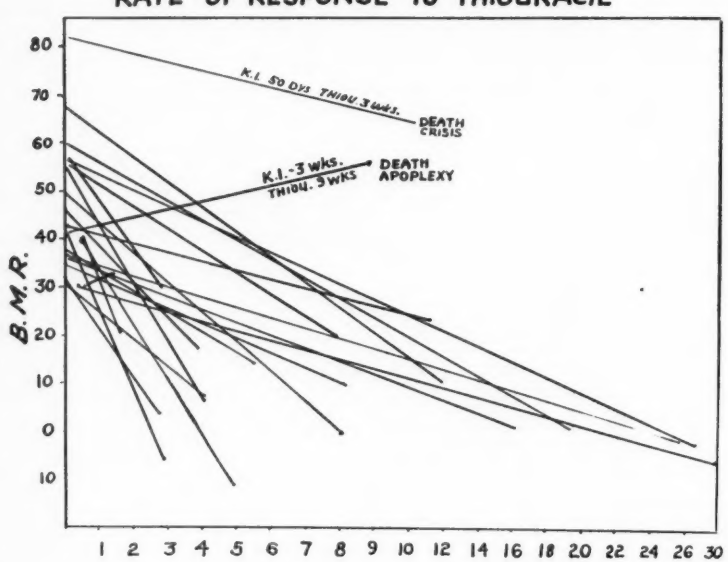

Chart 2

SYMPTOMS

The symptoms of hyperthyroidism disappear at about the same rate as the metabolic rate falls. The subjective symptoms are the first to be affected, disappearing in a few days in those patients who respond rapidly. There is usually a lag in the disappearance of the tachycardia present, and weight gain may not appear until the metabolic rate

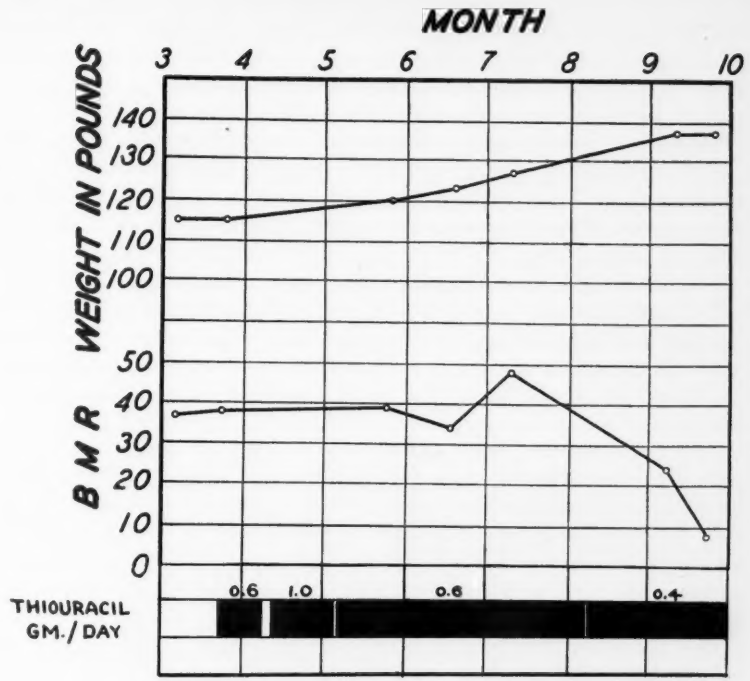

Chart 3

begins to approach normal if the patient is allowed to follow his own inclinations in eating. However, weight gain can be forced from the beginning in almost all patients if the caloric intake is high enough. By giving as much as 4000 calories per day we have seen gains of as much as 20 pounds in weight while the metabolic rate was 40 per cent or more above normal.

Exophthalmos appears to be relatively unaffected by thiouracil therapy. In most cases it does not increase, as might be expected according to existing theories. It may increase and decrease in the same patient during prolonged thiouracil therapy. Until the mechanism of its production is better understood, hypometabolism should be avoided during the use of thiouracil. Williams and Clute[15] have observed the continued increase in malignant exophthalmos and the occurrence of corneal ulcers during thiouracil therapy.

Cardiac decompensation tends to disappear gradually with the control of hyperthyroidism. Five of our patients had auricular fibrillation

which disappeared on thiouracil and digitalis in 2 and persisted in 3. McGavack[16] mentions 10 cases of fibrillation, 6 of which reconverted to a normal rhythm on thiouracil alone. Brawny edema is likely to remain, and peripheral edema may occur as a result of the drug.

Diabetes tends to become less severe during thiouracil, just as it does after thyroidectomy. In one of our patients on a constant diet we observed a fall in insulin dosage from 310 units to 60 units per day during therapy. Early in the treatment approximately 310 units were used daily for several weeks.

The size of the thyroid gland often increases after six or eight weeks of therapy. Such an increase was noted in 5 of our analyzed cases. The enlargement is usually mild. The gland tends to be solid at first, and in the diffusely enlarged ones a thrill and bruit can often be heard after a few weeks of therapy. On the basis of experimental findings thyroid feeding has been used to prevent such thyroid enlargement. Good results have been reported. Several small doses of iodine have been much more effective in reducing the vascularity, though we have seen little effect on gland size. In 2 of our patients the goiter increased enormously in size. In 1 of these, desiccated thyroid was given and, in error, the patient took 4 grains per day for a month. No change in size of the goiter was seen and the thrill and bruit remained pronounced. After taking 10 mg. of iodine per day for ten days the thrill and bruit were gone. In some cases after many months of thiouracil treatment the goiter may become quite soft.

At operation, glands of thiouracil-treated patients may be very bloody even after iodine treatment for some weeks preoperatively. Some glands, however, after ten to twenty days of iodine therapy are little, if any, more vascular than after iodine therapy alone. Microscopically they may show marked involution and evident retention of colloid.

REMISSIONS

It is evident that if a lasting remission cannot be brought about by thiouracil, and if the risk of surgery is not greater than the risk of using the drug, thiouracil is of no advantage to the patient. No one to date has been able to define any criteria by which to judge when the drug may be stopped, in what cases a remission may be expected, or how long the remission will last. Remissions have been reported where treatment has been carried on for periods varying from two to sixteen months. In many patients it appears that an increase in thyroid activity occurs in a few days to a few weeks after discontinuing the drug. Astwood has mentioned 9 cases with remission lasting up to sixteen months. In Fishberg and Verzimer's 96 cases, remissions lasting as long as fifteen months

have been obtained in 16 per cent of the cases.[17] In our analyzed group remissions have occurred in 10 cases after one to twenty-five months of treatment and have lasted as long as fifty-two weeks. In 9 other cases an attempt was made to stop the drug, but it became necessary to resume it. After fifteen months of therapy a sharp increase in metabolic rate and symptoms was seen in 1 patient when she reduced the dose below 0.4 Gm. per day. In another patient a similar recurrence was seen after five months' treatment when the dose was reduced to 0.2 Gm. Williams,[18] in a series of 247 cases treated, has attempted to withdraw therapy and to maintain a remission in 100. In half of these it was found necessary to resume the treatment. It is generally agreed that thiouracil produces a more complete remission than any other previous form of medical therapy, but the total advantage is reduced greatly by its toxic effects.

TOXIC EFFECTS

Toxic effects appear in 14 to 20 per cent of cases treated. Various estimates place the frequency of toxic effects at about 15 per cent and agranulocytosis at about 1 to 2 per cent. In many the toxic effects are mild. In most the drug can be used in decreased dosage without a return of symptoms. Toxic reactions apparently are more apt to occur (a) with large daily doses, (b) in severely ill patients, and (c) when the drug has been stopped for intervals and repeated.

TOXIC EFFECTS OF THIOURACIL

Mild	Moderate	Severe
Headache	Nausea	**Agranulocytosis**
Malaise	Vomiting	Thrombocytopenia
Chilliness	Diarrhea	Purpura
Itching	Jaundice	Hematuria
Sweating	**Fever**	Psychosis
Myalgia	Urticaria	
Anorexia	Rash	
Aphthous ulcers	Painful joints	
Conjunctivitis	Edema legs-eyes	
	Leukopenia	
	Dental abscesses	

The table shows some of the toxic effects noted in the literature. Toxic reactions were seen in 20 of our first 100 patients. In only 1 of these was it impossible to continue either thiouracil or thiobarbital. In 1, which has shown the most brilliant result, severe diabetes, severe hyperthyroidism, and cardiac decompensation were present. On 0.6 Gm. of thiouracil the white blood count promptly dropped to 2000, and

neutrophiles to 20 per cent. After beginning with 0.1 Gm. the dose was gradually increased and a good result obtained. In another chronic glomerulonephritis was present before therapy. After 17 weeks of treatment the white count fell to 2350, and neutrophiles to 19 per cent. Subsequently she took the drug, and it controlled her hyperthyroidism moderately well, while the white blood count rose to 4300. She later died of uremia and what appeared clinically to be thyroid crisis.

Of more than 5700 cases known to have been treated with thiouracil there have been 21 deaths from agranulocytosis, about one-third of 1 per cent, and granulopenia has occurred in approximately 3 per cent. It is worth remembering that granulopenia is a typical feature of hyperthyroidism, accounting for the relative lymphocytosis which is so frequently seen. Agranulocytosis is most apt to occur early in the course of therapy, but it has been reported after three months and one week. In one case it appeared 1 month after stopping the drug.

When severe agranulocytosis appears, the treatment of choice is (1) discontinuance of thiouracil, (2) transfusions, and (3) generous use of penicillin, 300,000 to 500,000 units daily.

In mild or uncomplicated cases of hyperthyroidism the risk of surgery in good hands is little, if any, greater than the risk of thiouracil alone. There is, therefore, no need to add to the total risk of these patients by giving thiouracil. In severely ill or complicated cases, however, the situation is quite different. In them the good to be obtained from the complete control of all hyperthyroidism is so great in comparison to a risk of one-third of 1 per cent that no question remains as to the advisability of giving the drug.

PREOPERATIVE USE OF THIOURACIL

We have chosen, therefore, for the present to reserve thiouracil for those patients whose safety is to be distinctly increased by using thiouracil, or for those who refuse surgery. Patients for whom we recommend thiouracil include those who are poor risks because of (1) old age and severe hyperthyroidism, (2) poor general health and severe weight loss, especially in elderly people, (3) cardiac decompensation or cardiac status in which mild degrees of hyperthyroidism may add distinctly to the surgical risk, (4) hyperthyroidism with deep intrathoracic extension of the goiter, severe tracheal compression or asthma, (5) hyperthyroidism with a history of one or more previous operations, and (6) patients who have been treated over long periods with iodine and who cannot obtain further improvement by its use. As improvement occurs each patient's problem must be judged on an individual basis. Some will remain in remission and require no therapy; in others the risk of surgery may still

be great, and continued use of thiouracil will be the treatment of choice. In others, operative surgery may be desirable, and the risk may be reduced by thiouracil to the point where this is feasible. When thyroidectomy is anticipated after thiouracil has been used, Lugol's solution may be given for three weeks before the day of operation, and thiouracil discontinued completely for at least one week preoperatively, as recommended by Lahey and Bartels.[19,20] Later, if distinctly safer drugs are obtainable, the question of choice of treatment will depend chiefly on the consistency with which lasting remissions can be obtained.

OTHER RELATED DRUGS

It is obvious that a safer drug is needed to replace thiouracil. Thiobarbital[21] has already been used in several hundred cases over periods up to several months. Unfortunately, its toxic effects are similar to those seen from thiouracil. Three cases of agranulocytosis have been seen with one death. We have 10 cases in which thiobarbital has been tried, and these were patients in whom toxic effects from thiouracil appeared. One developed fever and nausea with thiouracil and also with thiobarbital. In 1, aphthous ulcers recurred repeatedly on thiouracil but did not on thiobarbital. In the others thiobarbital was well borne and was effective in doses of 150 mg. per day or less. Other related drugs that are under investigation at present include normal ethyl thiouracil, propyl thiouracil, and butyl thiouracil. Astwood and VanderLaan have recently reported the use of ethyl and propyl thiouracil. The former was used in 14 patients, the latter[22] in 29. One uritarial reaction was encountered with the ethyl derivative and no side effects were noted with the propyl. The recommended doses were 25 mg. every eight to twelve hours to control hyperthyroidism and 25 to 50 mg. per day to maintain such control. No untoward side effects have been seen in the first 20 cases treated by propyl thiouracil in this Clinic in spite of the fact that one of these patients had disturbing symptoms following the administration of both thiouracil and barbital. If these drugs proved effective in non-toxic doses, lasting remissions will probably be frequent enough to increase the usefulness of the method greatly. Para-aminobenzoic acid has been tried with some promise.[23] So far the reported cases have responded slowly and corroboration is needed.

THIOURACIL IN OTHER CONDITIONS

The use of thiouracil in certain cases of arterial hypertension and in angina pectoris is a natural development following the use of total thyroidectomy for these diseases. A few good results have been reported,

but on the whole they are not impressive. Some promising results have been reported in thyroiditis.[24]

SUMMARY

In general it can be stated that the chief value of thiouracil and related substances is that complete control of all types of hyperthyroidism can be obtained by their use, and the patient can remain ambulatory except for complications. Their chief disadvantage is that they cause granulopenia in about 3 per cent of the cases and death in perhaps one-third to one-half of 1 per cent. For this reason patients must be kept under the most careful prolonged observation. Whether the use of thiouracil or related substances will bring about a large enough proportion of lasting remissions of hyperthyroidism to supersede surgery as treatment is not known. Until this knowledge is established, thiouracil should be reserved for those patients who can be treated more safely with the help of the drug than by the established methods.

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TYPHOID SHOCK THERAPY

Results of Fifteen Years' Experience

JOHN TUCKER, M.D.

A survey of the medical literature for the past five years reveals that the use of typhoid shock therapy is less popular than during the preceding decade. This is probably due to lessened need for non-specific protein in treatment of infections and inflammatory processes. This is indicative of medical progress and reflects better understanding of the cause and treatment of disease. Yet in spite of the amazing bactericidal and bacteriostatic effects of the sulfa drugs and penicillin, we are confronted still with many medical conditions which are refractory to ordinary therapy. It is among these that nonspecific protein shock therapy has a useful place in clinical medicine.

In some instances typhoid vaccine given subcutaneously or intravenously merely relieves painful symptons, but in many cases it shortens the course of disease and contributes to recovery. Experience with its use in several thousand patients during a fifteen-year period has determined the course of administration and indications and contraindications for its use.

We know relatively little about chemical and biological changes that take place in the body during this type of shock therapy. However, it can be rightfully assumed that fever produced by proteins injected intra-

venously or subcutaneously causes active participation of cells of the body in production of a rise in body temperature. Furthermore, experience leads me to believe that defenses of the body against infection are mobilized not only by increased cellular oxidation but also by modification of cellular permeability, increased chemical exchange between the cells and body fluids, and favorable effect on the formation of defensive enzymes and antibodies. Many investigators have emphasized these effects and have shown that following such shock reactions there is increase in total leucocytes and improved phagocytosis as well as improvement in minute volume of blood through the capillaries.

The favorable effects of intravenous typhoid therapy point to increase in the defense against diseases which have remained at a subacute or chronic level. On the other hand, except in cases of Sydenham's chorea, the results are rarely dramatic.

Production of fever by typhoid shock has certain advantages over passive hyperthermia induced by the heat cabinet. In the latter form of therapy discomfort and dangers from prolonged maintenance of high body temperature have led me to discontinue its use. In experience at Cleveland Clinic few, if any, diseases have been found that cannot be treated with greater benefit by typhoid vaccine or by therapeutic methods other than the hypertherm.

In an earlier trial with various methods of administering typhoid vaccine intravenously a definite therapeutic program proved to be essential for safe and satisfactory results. The principles of treatment outlined by Howard were those adopted.[1]

Formerly typhoid and paratyphoid vaccines as found in the open market were routinely employed, but in recent years a vaccine prepared in the Clinic laboratories has afforded better and more uniform results.

The routine treatment begins with an initial dose of 25 million typhoid and paratyphoid organisms for adults and 15 million for children under 10 years. The bacteria are diluted in 10 cc. of sterile physiologic saline solution and given in the vein of the forearm. In one to three hours the patient has a chill followed by fever of 102.5 to 103. If a chill does not occur promptly, it may be because the patient is refractory or the injection has been given extravenously. Under such conditions the chill may not occur until a second dose is administered.

With prompt rise in temperature the patient has no feeling of depression but rather the sensation which accompanies a slight attack of "flu." Within two or three hours the fever may drop rapidly or be followed by a secondary rise. As soon as the temperature remains fairly normal for twenty-four hours, the second dose, consisting of 50 million bacteria, is given. Each subsequent dose is double the preceding dose

until a total of six injections has been administered. In other words, the adult patient receives successively 25 million, 50 million, 100 million, 200 million, 400 million, and 800 million. An afebrile period of approximately twenty-four hours is allowed to elapse before the next dose is given.

From a careful selection of cases, there have occurred no serious, unfavorable effects with use of intravenous typhoid vaccine in either children or adults. Among the contraindications to its use, however, are such conditions as advanced arteriosclerosis and hypertension, myocardial weakness, angina pectoris, chronic renal disease, diabetes mellitus, active tuberculosis, severe allergy, and pronounced undernourishment with fatigue. In acute rheumatism or chorea the presence of carditis or endocarditis does not increase the hazard of treatment.

The advantages of this treatment are:

1. Safety.
2. Economy—approximately two weeks hospitalization.
3. Little, if any dehydration.
4. Prompt reaction after injection of vaccine.
5. Active participation of the cells, resembling an immunizing process.
6. Repetition of the course of treatment without hazard; with intravenous method the patient does not seem to be sensitized to typhoid bacteria.

In dealing with clinical application of intravenous typhoid vaccine to certain disease processes it must be emphasized that this form of treatment does not lend itself to accurate statistical study. Many times one cannot be certain whether the patient is cured or merely relieved of uncomfortable symptoms. Furthermore, the disease may be still in progress or may recur at a later date. However, since this type of therapy is employed in conditions that may be unresponsive to other forms of treatment, and since many statements in this paper are based on fifteen years of experience, I have the temerity to be rather dogmatic.

Nonspecific shock has been produced in this Clinic for a multitude of pathologic states, but at present it is utilized largely in the following conditions.

1. Acute virus infections of the central nervous system—encephalitis and encephalomyelitis.
2. Chronic rheumatoid arthritis.
3. Chorea.
4. Various eye and skin disorders.

In untreated cases of acute encephalitis recovery occurs in almost 25 per cent while death occurs in slightly more than 38 per cent. Of the remaining 37 per cent there are mild or severe complications. Since the neurotrophic virus, whether chemical or bacterial, is an obligate parasite which lives and multiplies within the grey matter of the central nervous system, it is understandable why no specific treatment is available. The cell protoplasm of the host probably acts as a barrier to viricidal substances such as antibodies and chemicals. Theoretically nonspecific protein shock therapy by influencing cell metabolism might stimulate the grey matter to attenuate or destroy the virus.

In an effort to evaluate the results of intravenous typhoid injections we have not been able to make a satisfactory statistical study. This is due to several reasons among which are the relatively few cases of acute lethargic encephalitis that have come to the Clinic. Apparently this disease is not as prevalent in this locality as elsewhere. Then, too, the diagnosis is often difficult. Such conditions as benign lymphocyte choriomeningitis, acute disseminated sclerosis, and even brain tumors, especially in children, have caused some mistakes in early diagnosis. The general impression has been, however, that the fever induced by typhoid reactions has reduced headache, somnolence or irritability, and spinal fluid cell count within a week.

In the treatment of 49 patients with acute encephalitis by roentgen ray therapy Portmann found that 29 (59.1 per cent) recovered and 15 (30.6 per cent) improved. This treatment resulted in improvement in 13 cases as early as three or four days after radiation.[2] In 1 of these patients who recovered consciousness following x-ray therapy I administered a course of typhoid shock therapy. After the third reaction the patient became quiet and relaxed and completely recovered. Three other cases recovered even more rapidly with the combined roentgen ray and typhoid shock treatment.

In Sydenham's chorea, on the other hand, immediate results of typhoid therapy are often spectacular. After as few as two or three reactions the purposeless movements of the body are quieted, and the patient becomes generally subdued. While the average patient recovers from acute chorea in six to eight weeks without treatment, some patients included in this study are known to have had the disease for two to five months.

In a series of 29 patients with Sydenham's chorea treated at the Clinic recovery was obtained in 18 (67 per cent) after three to six shock treatments, decided improvement in 6 (23 per cent), and no relief in 3 (10 per cent). In this group 5 patients had had one previous attack;

1, two earlier attacks; and 1, six recurrences of short duration over a period of two years.

In our follow-up study only 2 patients had recurrences of chorea, and both had mild attacks. These excellent results may have been due, to a large degree, to carefully followed instructions given to the parents of the patient upon dismissal from the hospital.

The etiology of chronic rheumatoid arthritis is unknown. There is no evidence to prove that it is due to any known infection. Removal of infective foci is of little if any value. This serious, progressive, and deforming type of arthritis presents a most difficult and disappointing therapeutic problem. Gradual destruction of joint cartilage characterized by proliferation of the synovial membrane, small round cell infiltration and growth of granulation tissue over the joint cartilage usually ends in ankylosis.

Six years ago 40 cases treated with intravenous typhoid vaccine (six reactions) were reviewed. In 72.5 per cent of these there was immediate subjective relief resulting in amelioration of joint pain, restlessness, and fever. However, this improvement was not permanent, since it did not shorten the course of the disease or contribute materially to a "cure." But the patients who responded with temporary improvement were grateful for this relief and were content to remain in the hospital for special therapy, such as blood transfusion, neoarsphenamine, physical therapy, dietary regulation, and other measures to build up general resistance of the body. These shock treatments are used in patients who have acute exacerbations of rheumatoid arthritis, but rarely is it found necessary to give more than six successive typhoid injections at any particular attack.

In ophthalmology intravenous typhoid vaccine is administered in the following conditions:

1. Retrobulbar neuritis of unknown cause.
2. Infectious retinopathies which have failed to respond to other forms of treatment.
3. Keratitis and iritis of rheumatic origin.
4. Keratitis in congenital syphilis.
5. Uveitis with secondary glaucoma (before and after surgery).
6. Presence of foreign bodies (before and after surgery).

The results have warranted a continuation of shock therapy in the foregoing diseases. Likewise, nonspecific therapy with the use of typhoid vaccine or milk protein are employed with some frequency in dermatology. Persistent pustular acne and pyogenic dermatoses, severe

psoriasis, especially when accompanied by arthritis, and erythema nodosum improve as a rule after protein shock treatments in conjunction with other therapeutic procedures. Shock treatment has been discontinued, except in rare instances, in otolaryngology and urology.

It is obvious from this brief review of the experience of fifteen years with intravenous typhoid shock therapy that a strong endorsement of this measure cannot be presented. Yet in properly selected cases it is helpful, and in Sydenham's chorea it definitely hastens recovery. Until specific therapy is available for many diseases of doubtful etiology or those in which ordinary treatment is unsatisfactory, we are justified in utilizing nonspecific measures.

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THE USE OF TANTALUM FOR REPAIR OF CRANIAL DEFECTS IN INFECTED CASES

W. JAMES GARDNER, M.D.

The primary purpose of this article is to demonstrate that presence of a tantalum implant does not impair healing of an infected wound. Secondarily the author wishes to describe his experience with a hitherto untried method of dealing with abscess of the brain.

Tantalum, a newly available metal, has proved to be the most satisfactory material for repair of cranial defects.[1-10] Thus far it has been employed chiefly in secondary repair of cranial defects resulting from war wounds. A few surgeons have advocated its use in contaminated wounds, as in immediate repair of compound comminuated fractures of the skull.[11,12,13,14] Infection, however, has been generally considered an absolute contraindication to the use of any metal implant.

Treatment of brain abscess by complete excision rather than drainage has yielded a lower morbidity in the author's experience, but the danger of cerebral fungus following radical excision has been a deterrent to the universal application of this method. Since cerebral fungus can be entirely prevented by closure of the skull defect with tantalum, the use of this material naturally suggested itself. Furthermore, tantalum has proved so inert by past experience[13] that its use in infected cases seemed

entirely justifiable. In the past twenty months, therefore, tantalum has been used in 7 instances for closure of cranial defects resulting from excision of brain abscesses and in 1 case of acute osteomyelitis of the frontal bone. In this series there were six recoveries and two deaths. In 6 of the cases the wound healed by primary union, and in 2 infection occurred necessitating subsequent removal of the implant. The results indicate that if the responsible organism is sensitive to penicillin, and if the abscess is radically excised and the resulting cranial defect immediately closed with a tantalum implant, primary healing may be anticipated.

CASE REPORTS

Case 1*—A young man, aged 17 years, was hospitalized for three months after a frontal craniectomy for osteomyelitis of the skull complicating frontal sinusitis. During this time he had repeated operations for the drainage of brain abscesses of the left frontal and right occipital lobes. The organism was a penicillin-sensitive anaerobic Streptococcus. On June 27, 1944, the patient was extremely ill with meningitis and multiple brain abscesses in the right parieto-occipital region. On this date a flap of scalp was reflected and a bony opening 6.5 cm. in diameter was made over the site of the abscesses. The dura was excised, and the diseased brain was cut away with the electro-surgical loop to a depth of more than 5 cm. Several small subcortical abscesses were opened and removed. Palpation then disclosed a large firm subdural abscess adherent to the right side of the falx. This was incised, and about 2 ounces of thick pus escaped. The outer wall of this abscess was removed, and the medial wall was left attached to the falx. Ten cubic centimeters of penicillin solution, 1000 units per cubic centimeter, was introduced into the cavity in the brain tissue, after which a perforated tantalum implant was placed over the bony opening and fastened to the outer table of the skull with two tantalum screws. The dura was not closed. The scalp was then tightly closed with a buried tier of interrupted black silk stitches in the galea.† Drainage was not instituted. For the next forty-eight hours the patient received intramuscularly 10,000 units of penicillin every four hours; 10,000 units was injected beneath the scalp over the tantalum implant every four hours, and 10,000 units was given intrathecally every twelve hours. After forty-eight hours the intrathecal injections were discontinued and the injections beneath the scalp were reduced to twice a day. The latter injections and the intramuscular injections were continued until the sixteenth postoperative day. The temperature reached normal on the third day after operation and remained normal.

Convalescence was smooth, and the patient was discharged three weeks after operation. At no time was there any evidence of inflammation in the wound. When last seen fourteen months after operation he was free from symptoms and the cosmetic result was good.

Comment: This was the first case in which a tantalum implant was placed in an infected wound. The response to the operation was dra-

* This case was reported previously (ref. 13, case 15).

† The author has employed this method of closure of scalp wounds for many years. Careful placing of the subcutaneous sutures in the scalp renders skin sutures unnecessary and aids wound healing. Screws offer the best method of fastening the implant to the skull and, since properly sized tantalum screws are now available, all other methods should be considered obsolete. These methods of closure were employed in all reported cases.

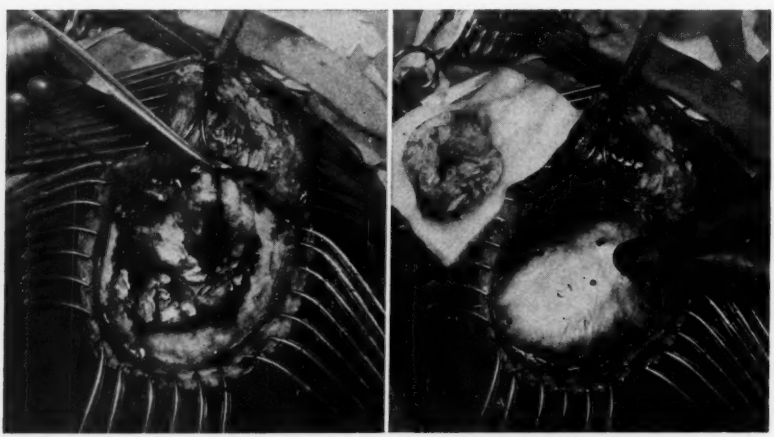
matic especially in view of the long illness and the apparent hopelessness of the situation at the time of operation.

Case 2—A woman, aged 33, was admitted to the hospital January 20, 1945, with a complaint of headache. January 3 she had developed a right earache followed by discharge of pus, and the following day she had a high fever. Transient numbness of the left arm and leg occurred January 15, and on this date the family physician started treatment by intramuscular injections of penicillin.

On admission the patient was confused and complained of headache. There was early edema of the optic disks and a left homonymous hemianopsia. Spinal fluid pressure was 340 mm. of water; fluid was faintly cloudy and contained 1000 cells per c. mm., 65 per cent of which were polymorphonuclear leucocytes and 35 per cent lymphocytes. Spinal fluid culture was sterile. The clinical diagnosis was acute right temporal lobe abscess. Patient was given 15,000 units of penicillin intramuscularly every three hours, and sulfadiazine, 1 Gm. four times daily by mouth. Spinal fluid pressure on February 12 was 200 mm. of water, and the fluid contained 25 lymphocytes per c. mm. The patient became more drowsy, the left homonymous hemianopsia was still present, and there was a paresis of left angle of the mouth. The abscess was now considered to be in a favorable state for operation.

February 14, 1945, through a short linear incision above the right ear, an opening was made in the bone with a cranial burr. A brain cannula encountered an abscess at a depth of 2 or 3 cc. Eight cubic centimeters of thick creamy pus escaped from the cannula. The abscess cavity was irrigated with 10 cc. of a 1-1000 penicillin solution, the cannula removed, and the wound closed. Pus contained Diplococcus pneumoniae type I in pure culture. Because of the favorable character of the organism, radical excision of the abscess was decided upon.

The following day a small curved flap of scalp was reflected above the right ear, and the previous bony opening enlarged with a rongeur to a diameter of 7 cm. The dura



a *b*

FIG. 1. Case 2. (a) The collapsed abscess has been dissected free except for its stalk. (b) The tantalum implant ready for fastening in place.

was incised, and the brain cortex overlying the wall of the abscess removed. A globular abscess approximately 6 cm. in diameter and attached by a short stalk to the dura on the upper surface of the petrous bone was freed from the surrounding brain and the dura by blunt dissection (fig. 1(a)).

The temporal horn of the ventricle was opened during the dissection and the abscess wall ruptured during its removal, spilling a large quantity of thick creamy pus. The resultant brain cavity was irrigated with saline solution. The dura was not closed. A perforated tantalum implant, 8 cm. in diameter, was fashioned and fastened over the skull defect (fig. 1(b)). Five grams of sulfanilamide crystals was placed on the outer surface of the implant. Scalp was closed in the usual fashion without drainage. Twenty-five thousand units of penicillin solution was then injected between the scalp and the implant. During the next forty-eight hours the patient received four intravenous injections of 50,000 units of specific pneumococcus type I antiserum and four injections of 20,000 units of penicillin beneath the scalp. In addition she received 15,000 units of penicillin intramuscularly every three hours, and 1 Gm. of sulfadiazine by mouth every four hours for sixteen days.

For two weeks 30 to 60 cc. of blood-tinged fluid was aspirated from beneath the scalp daily. On the first and second postoperative day cultures of this fluid disclosed B. coli communis, but subsequent cultures were sterile. Patient was discharged from the hospital March 3, free from symptoms except for left homonymous hemianopsia. When last examined eleven months after operation, she was in excellent health. There was still a left homonymous field defect.

Comment: This patient, in addition to penicillin and sulfonamides, received intravenously specific pneumococcus antiserum, which undoubtedly was a factor in her recovery.

Case 3—A boy, aged 6 years, was struck in the right eye with a snowball January 12, 1945. The following day he became drowsy, and two days later his temperature was 104 F. January 18 a right orbital abscess was drained, and January 19 he had a convulsion.

February 2 he was admitted to the hospital because of continued drowsiness and vomiting. Temperature, pulse, and respiration were normal. The right upper eyelid was swollen and indurated, and a small sinus persisted from drainage of the orbital abscess. There were no neurologic signs. X-rays of the skull disclosed clouding of the right antrum and ethmoid sinuses. The clinical diagnosis was right frontal lobe abscess secondary to sinusitis and orbital abscess. With the use of penicillin, 15,000 units given intramuscularly every three hours, he became alert and vomiting ceased.

February 13 he complained of headache in the right frontal region. February 19 bilateral papilledema was discovered, and a Babinski response appeared in the left foot. Operation was now deemed advisable.

February 19 a small flap of scalp was reflected from the right frontal region down to the supraorbital ridge. A bony opening 7 cm. in diameter was made with a rongeur. An exploring needle encountered a large abscess at a depth of 1 cm. beneath the cortex. Forty cubic centimeters of thick foul pus was aspirated from the abscess, after which the abscess wall was exposed by a cortical incision. The abscess was still too large to be removed through the bony opening. Incision was therefore made into the abscess cavity, and the contents removed with an aspirator. The incision in the wall of the abscess was closed with a hemostat, and by gentle traction and blunt dissection, the abscess wall was removed without further rupture (fig. 2). A stalk of fibrous tissue connected the abscess wall to the floor of the anterior fossa of the skull lateral to the olfactory groove. This was

freed readily by blunt dissection leaving a small area of roughened but otherwise intact dura. The cavity was irrigated with warm saline, and the dura was loosely closed. The bony opening was repaired with a perforated tantalum plate. Fifteen thousand units of penicillin was instilled into the brain cavity; 5 Gm. of sulfanilamide was placed on the outer surface of the implant, and the scalp was closed.

Pus culture revealed Streptococcus salivarius. For ten days the patient was given intramuscularly 15,000 units of penicillin every three hours, and oral sulfadiazine 1 Gm. four times daily. The first three days the scalp over the implant was tapped daily, a small amount of bloody fluid removed, and 15,000 units of penicillin instilled beneath the scalp. Thereafter no fluid collected, temperature was normal, convalescence was uneventful, and the patient was discharged from the hospital March 4 (fig. 3). Patient was readmitted to the hospital March 12 with a temperature of 102 F. and symptoms of meningitis. Spinal fluid pressure was over 700 mm. of water; fluid contained 800 polymorphonuclear cells; culture was sterile. Patient was treated with daily spinal puncture, intrathecal and intramuscular penicillin and sulfadiazine. He improved for a time but on March 24 became irrational. A needle, introduced through the scalp and through one of the tantalum plate perforations into the right frontal lobe, encountered a large abscess beneath the cortex. Seventy-five cubic centimeters of thick pus was aspirated; culture again revealed Streptococcus salivarius.

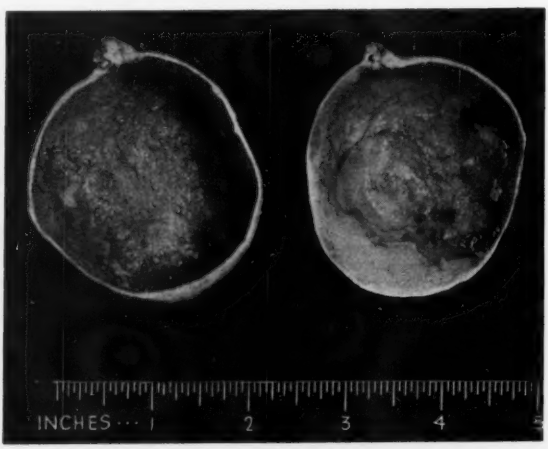


Fig. 2. Case 3. The abscess capsule after fixation.

March 29 the patient was reoperated upon. The tantalum implant appeared to be in perfect condition, enclosed in a smooth-walled membrane containing no fluid. The implant was removed, and a large irregularly shaped subcortical abscess was excised. The abscess wall was found attached to a circular area of dura on the floor of the anterior fossa lateral to the olfactory groove. The abscess wall was thin and contained many irregular ramifications, so that it was not possible to remove it entirely. The cavity was irrigated with saline, the tantalum plate reapplied, 50,000 units of penicillin injected into the cavity, and the scalp closed. A needle was inserted beneath the scalp at the

operative site for drainage and injection of penicillin. Patient did not rally and died thirty-six hours later.

Necropsy disclosed no pus in the ethnoid or sphenoid sinuses. There was marked edema of the contents of the right orbit with an area of erosion of the roof, 8 mm. in diameter. There was a small abscess of the head of the right caudate nucleus which had ruptured into the anterior horn of the right ventricle. It appeared that the brain abscess was secondary to infection within the orbit.

Comment: In retrospect it appears that recurrence of the abscess in this case could have been avoided by the more vigorous administration of penicillin. The total dosage was less than that given any other patient. This was due in part to the patient's terror of the needle.

The innocuous nature of tantalum is attested by the fact that the wall of the recurrent abscess reached to within a few millimeters of the

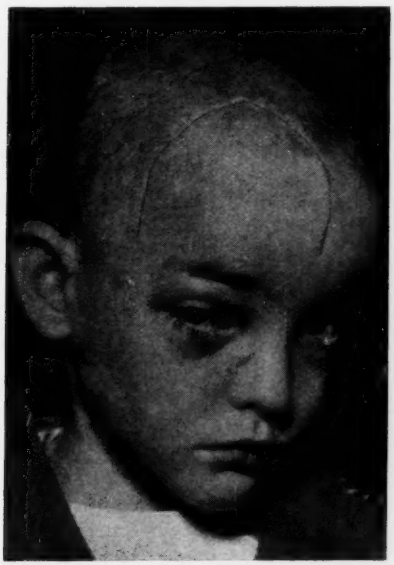


FIG. 3. Case 3. Wound healing on eleventh postoperative day.

inner surface of the implant and did not enclose it. It would certainly appear that the recurrence of the abscess was in no way due to the presence of the implant.

The lack of inclusion of the tantalum implant in the abscess cavity in spite of its proximity to the infectious process in this case suggested the possibility that tantalum might have an actual inhibiting effect upon

the growth of bacteria. In order to investigate the possibility, Dr. L. W. Diggs, director of the Department of Clinical Pathology, Cleveland Clinic, made the following studies.

1. Two blood plates were streaked with slant cultures of B. coli and one with Staph. aureus. Six to 8 sterile pieces of tantalum 3 mm. in diameter were dropped on the surface of each plate. The slants were incubated and observed at 24, 48 and 72 hours. The culture was satisfactory in all three plates. There was no evidence of inhibition of bacterial growth in the neighborhood of any of the pieces of tantalum.

2. Eight tubes containing brain-heart infusion broth were innoculated with 0.1 ml. of Staph. aureus suspension in saline. Two pieces of tantalum were placed in one tube, 4 in another, 8 and 20 in the third and fourth tubes, respectively. The other four tubes served as control. After 24 hours' incubation the broth was cloudy in all tubes, with no apparent inhibition of growth in the tubes containing 2, 4, 8 and 20 pieces.

3. Ten tubes of brain-heart infusion broth were innoculated with one drop of B. coli suspension. Two pieces of tantalum were placed in one tube, 9, 17 and 19 pieces in the second, third and fourth tubes, respectively. One of the tubes was placed in the icebox; the others were incubated. The growth rate as revealed by the turbidity changes in the ten tubes showed that the presence of pieces of tantalum had no effect on the rate of growth.

From these results it is concluded that the tantalum pieces had no apparent effect either as to inhibition or stimulation of the growth of Staph. aureus or B. coli on the mediae used and under the conditions outlined above.

Case 4—A young man, aged 17, was admitted to the hospital May 8, 1945, complaining of frontal headache. April 8 he developed headache and fever and was treated with penicillin. May 1 a swelling of his forehead appeared.

Patient was afebrile, mentally dull, and apathetic. There was doughy swelling above the frontal sinuses. X-ray of the skull showed clouding of both frontal sinuses and some mottling of the frontal bone just above the sinuses. Spinal fluid pressure was 580 mm. of water; fluid contained 35 cells, 95 per cent of which were lymphocytes. Clinical diagnosis was osteomyelitis of the frontal bone and brain abscess secondary to frontal sinusitis.

May 14, 1945, a curved flap of scalp was reflected from the frontal region down to the eyebrows, and a large periosteal abscess was evacuated. An eroded area of the skull just above the frontal sinus was exuding pus. Frontal bone was removed with a rongeur almost back to the coronal suture, together with upper portions of both frontal sinuses. Granulation tissue was present on the outer surface of the dura at the tip of the left frontal lobe. A cannula encountered thin foul-smelling pus at a depth of 2 cm. beneath the dura. A perforated implant was fashioned to cover the bony defect. An opening about 1 cm. in diameter was made in the implant over the site at which the abscess had been tapped. Five grams of sulfanilamide was placed on the outer surface of the implant, and the scalp was closed (fig. 4-5).

A stab wound was made over the opening in the implant and through it into the abscess cavity a cannula was inserted. A ureteral catheter was passed through the cannula for constant irrigation of the abscess cavity with dilute solution of penicillin. Culture of the pus disclosed Alcaligenes faecalis and Streptococcus faecalis. For four days the abscess cavity was irrigated continuously with a solution of 100 units penicillin per cc. saline, and then the cannula was removed.

On May 18 the wound was reopened because a clot had formed between the tantalum inplant and the scalp. After evacuating the clot, the wound was closed with through and through sutures about a rubber tissue drain. Penicillin was introduced beneath the scalp daily for four days. It was then discontinued and the drain removed. May 22, 25, June 2 and 4, fluid aspirated daily from beneath the scalp contained B. alcaligenes faecalis. After the last date the fluid ceased to accumulate, and patient was discharged June 10. The patient received intramuscularly 15,000 units of penicillin

every three hours throughout his hospital stay together with 4 to 6 Gm. of sulfadiazine by mouth. When he was last heard from eight months after operation there were no symptoms, and the cosmetic result was excellent (fig. 6).

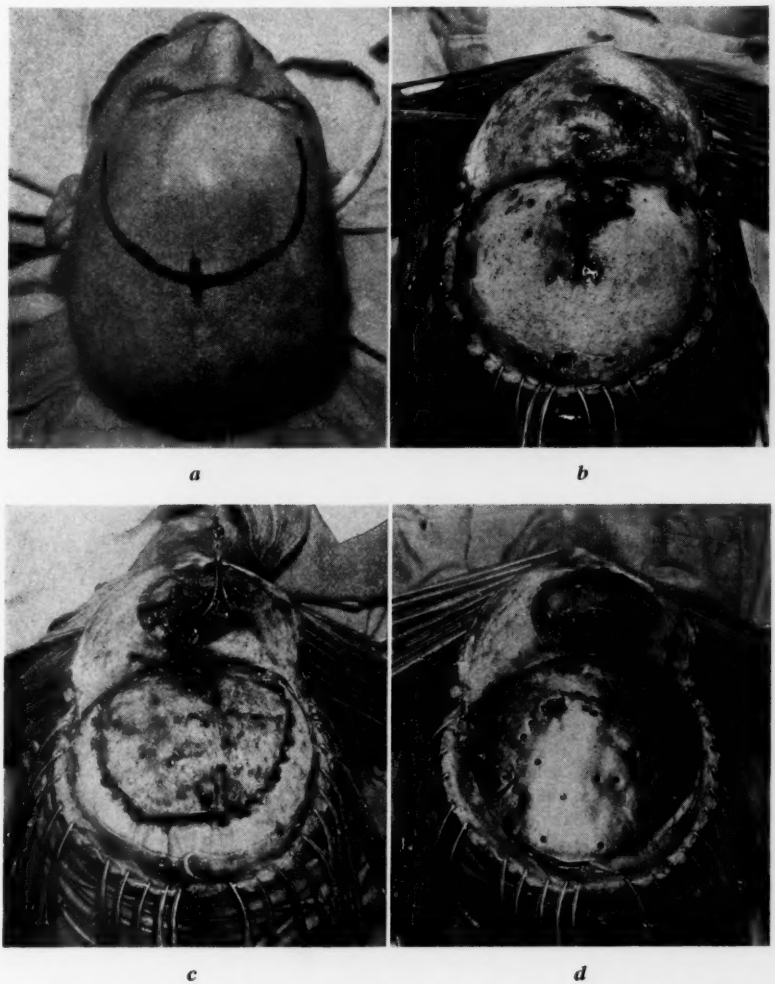


FIG. 4. Case 4. (a) Location of the incision. (b) Scalp has been reflected disclosing subperiosteal abscess. (c) Infected bone has been removed, including the upper portion of the frontal sinuses. Extradural granulation tissue is present over tip of left frontal lobe. (d) Tantalum implant in situ. The large perforation was made to permit insertion of cannula for drainage of brain abscess.

Comment: This is the most significant case in this series. Osteomyelitis of the frontal bone secondary to sinusitis carries a very high morbidity when treated by the usual method of removing the infected bone and leaving the scalp widely open. The result in this case was so gratifying that this method certainly deserves further trial. Even in case continuation of the infection should necessitate subsequent removal of the implant the patient will have lost nothing. The presence of the implant controls the abnormal pulsation of the uncovered brain and this splinting of the wound aids its healing.

FIG. 5. Case 4. Cosmetic result five and one half months postoperative.

Case 5—A man, aged 49, had history of a draining left ear for forty years. April 11, 1945, he developed a chill and increased flow of pus from left ear. He was treated with penicillin and sulfadiazine. Stupor developed on May 6.

On admission to the hospital, May 8, patient was afebrile, semistuporous, aphasic, and there was pronounced choking of the optic disks. The left ear canal contained polyps and was discharging pus. The stupor lightened somewhat after a week's treatment with sulfonamides and penicillin, and a right homonymous hemianopsia was demonstrated. Diagnosis was abscess of the left temporal lobe.

May 15, a flap of scalp was reflected from the left temporal region, and a bony opening 8 cm. in diameter was made. Just above the mastoid an epidural abscess containing 6 to 8 cc. of thick pus was evacuated. Thickened dura at this point was adherent to the brain underneath. Dura was incised disclosing a fibrous stalk leading from the involved dura to a large abscess in the temporal lobe 1 cm. beneath the cortex. The abscess wall, which ruptured during removal, must have originally contained 3 to 4

ounces of pus. The abscess wall was excised in its entirety. The involved dura was likewise excised leaving a defect about 6 cm. in diameter. There was roughening of the superior surface of the outer portion of the petrous bone.

A perforated tantalum implant was fashioned and was fastened over the bony opening. The dura was not closed. The wound was flooded with penicillin solution, 1000 units per cc., and 5 Gm. of sulfanilamide was placed on the outer surface of the tantalum implant. The temporal muscle was repaired and the scalp closed. Two 18 gage needles were introduced through the scalp to the outer surface of the implant and through them the wound was irrigated continuously for the next five days with a saline solution of penicillin, 100 units per cc. Pus culture contained anaerobic Streptococcus and Proteus vulgaris. Patient was given orally sulfadiazine 4 to 6 Gm. daily, and intramuscularly penicillin, 20,000 units every three hours.

The patient's condition slowly improved but fluid aspirated from beneath the scalp at the operative site contained Proteus vulgaris. This fluid became purulent, and on May 31 the scalp wound was incised and drained and a left radical mastoidectomy performed. A collection of pus was found in the mastoid cavity, and through a bony dehiscence an extradural abscess was evacuated from the posterior fossa. The scalp wound and ear continued to drain. June 15 the scalp flap was reflected and the tantalum implant removed. A thick layer of granulation tissue was present on the outer surface of the newly formed dura. This granulation tissue was removed with a curet and the wound closed with through and through sutures about a rubber tissue drain. Patient was discharged from the hospital August 4. Because of lack of apposition of the wound surfaces, healing was slow. After continued use of pressure dressing, healing was finally complete on October 9. The patient returned to work on November 30. He was free from symptoms and the visual fields were normal. Drainage from the ear had ceased.

Comment: In this case, the mixed infection in the contiguous mastoid process and the chronic discharge from the ear canal, precluded the possibility of primary healing. The implant was introduced as a temporary expedient to prevent cerebral fungus and to encourage the local walling off of the infection.

Case 6—A boy, aged 15, had a discharging right ear for three years. He had been subject to headaches for two months and had been treated on two occasions in another hospital for meningitis with penicillin and sulfonamide. Three days prior to entry his consciousness became clouded. He was admitted to the hospital August 8, 1945, with temperature 101.5 F. He was stuporous with bilateral papilledema, right third nerve paralysis, and a discharging right ear. Spinal fluid pressure was over 700 mm. of water; fluid contained 800 leukocytes, 75 per cent of which were polymorphonuclear. Diagnosis was abscess of right temporal lobe.

An hour after entry, the right temporal region was trephined. The brain cannula encountered the abscess at a depth of 3 cm. Thirty cubic centimeters of foul pus was evacuated after which the cavity was irrigated with saline and 30,000 units of penicillin in 3 cc. of saline was then introduced into the abscess cavity. Cannula was removed and the wound closed. Culture of the pus disclosed Bacillus coli and Staphylococcus albus. Forty-eight hours later the patient experienced a sudden respiratory arrest. Retapping of the abscess released 2 ounces of thin pus, and respirations were re-established. It was decided to excise the abscess. A scalp flap was turned down in the right temporal region, and an opening in the temporal bone about 6 cm. in diameter was made with a rongeur. Dura was incised and an incision made through the brain cortex down to the abscess wall. The abscess wall was removed in its entirety by blunt dissection, although it was

ruptured during the process. A narrow but firm stalk anchored the abscess wall to the petrous ridge. The bone here, however, was not exposed. A perforated tantalum implant was placed over the bony defect. The dura was not closed. Five grams of sulfanilamide was placed in the brain cavity with 30,000 units of penicillin in 3 cc. of solution. The wound was closed. Fluid which continued to collect beneath the scalp over the implant was aspirated each day for ten days and penicillin was injected. The patient was also given intramuscularly 30,000 units of penicillin every three hours for twenty-five days and orally was given sulfadiazine. Fluid from beneath the scalp became progressively more turbid until it was decidedly purulent. Culture of this fluid showed consistently a pure growth of B. coli. August 24, through and through drainage of the scalp wound was established and the wound irrigated once every hour for several days with a 1-10,000 phenyl mercuric borate solution. Patient was out of bed and offered no complaint, but the scalp and the ear continued to drain.

September 11, a right mastoidectomy was performed and a cholesteatoma was removed from the mastoid antrum. September 19, the previous scalp incision was reopened and the tantalum plate removed. A thick layer of granulation tissue on the dense newly formed dura and on the under surface of the scalp was removed with curet. Wound was closed with through and through silk worm gut suture about a single rubber tissue drain. Convalescence was satisfactory and the patient was discharged from the hospital September 30, 1945. On October 27 the scalp wound and ear canal had ceased draining and the patient was sympton free. Perimetric study disclosed an upper left homonymous defect.

Comment: In this case, as in the previous one, primary healing was not anticipated, but the temporary presence of the implant prevented cerebral fungus and aided the patient's recovery.

Case 7—A man, aged 36, was admitted to the hospital July 28, 1945. July 10 he had chills, fever, and generalized aching, and was treated for "grippe." July 14 he had developed headache, tingling, and weakness of the left arm, and an impairment of the left field of vision. He was admitted to another hospital July 18, where the spinal fluid pressure was found to be 15 mm. of mercury. Fluid contained 690 cells, 60 per cent of which were polymorphonuclear. Temperature was 102.2 F. He was treated with penicillin and sulfadiazine; fever subsided, but the hemianopsia and weakness of the left arm persisted, with extension of this weakness to the left leg.

On admission the patient had mild papilledema, a complete left homonymous hemianopsia, a pronounced left hemiparesis involving face, arm, and leg, with astereognosis and loss of sense of position. Spinal fluid pressure was 500 mm. of water. Spinal fluid contained no cells. Diagnosis was right temporoparietal abscess from some undetermined focus, probably metastatic from the lungs.

Due to comparatively recent formation of the abscess, surgical intervention was delayed for a time in order to obtain more thorough encapsulation. Patient was placed on 30,000 units of penicillin intramuscularly every three hours, and oral sulfadiazine.

August 8, a right temporoparietal craniotomy was performed. A cannula located the abscess in the parietal lobe considerably higher than was anticipated. The scalp incision was carried higher and the bony opening extended upward with a rongeur to expose the abscess site. Cortex and abscess wall were incised, pus removed, and the abscess wall excised. The abscess appeared to originate in the center of the parietal lobe and had no dural attachment. After removal the large bony opening was covered with a perforated tantalum implant. Dura was left widely open, 30,000 units of penicillin was introduced beneath the implant, and the wound was closed. Examination of the

pus disclosed Streptococcus mitior in pure culture. Penicillin was continued intramuscularly and sulfadiazine orally. For three days 30,000 units of penicillin was injected beneath the scalp daily. Patient remained afebrile following operation and became more alert, but on the fifth postoperative day the left hemiparesis became complete. Wound healed by primary union, and the patient was discharged August 26. He was readmitted August 31, with chills, headache, stiff neck, and a temperature of 101 F. Spinal fluid, normal just prior to discharge, was cloudy and pressure was 350 mm. of water. This fluid contained 5000 polymorphonuclears. The culture was sterile. Patient was placed on 50,000 units of penicillin, given intramuscularly every three hours, and sulfadiazine given orally. Daily spinal punctures were performed and fluid remained cloudy until September 11. September 19, the patient still complained of headaches. Suspecting a recurrent brain abscess, I introduced a needle through one of the tantalum plate perforations, but no pus was encountered. September 25 an encephalogram was made. Films showed a slight shift of the ventricular system to the left side. Patient continued to complain of headaches, and there was no improvement of the left hemiplegia.

October 5 the previous scalp flap was reflected and the tantalum implant removed. There was neither fluid nor any evidence of infection about the implant. Part of the exposed brain was covered by the original dura. The upper portion of the exposed brain was covered merely by thin, transparent, newly formed dura. Multiple punctures with a brain cannula in the parietal, frontal, occipital, and temporal lobes failed to disclose an abscess. The tantalum implant was replaced and the scalp closed. Patient's convalescence was satisfactory and his headaches relieved. He remained afebrile and the wound healed by primary union. The patient was discharged October 13.

He was readmitted October 25, 1945, with recurrence of headache and fever. Once more a needle was introduced through one of the perforations in the tantalum implant and this time an abscess was encountered in the posterior inferior portion of the occipital lobe. Seventeen cubic centimeters of pus was removed, and 30,000 units of penicillin was injected into the cavity. During the operation the patient was given 1,000,000 units of penicillin intravenously, and from then until his death he received 400,000 units of penicillin daily, either intramuscularly or intravenously. Sulfadiazine was given orally or intravenously daily, the blood level varying between 4.0 and 20.5 mg. per 100 cc.

The patient did not improve, and it was apparent by this time that he had multiple abscesses in the right cerebral hemisphere. On October 31, 1945, it was decided to remove the right cerebral hemisphere in an effort to preserve life. On reflection of the scalp, the tantalum implant was found in good condition with no evidence of infection about it. The implant was removed, the bony opening enlarged, and the hemisphere removed. A firm mass was palpable in the tip of the temporal lobe but no pus was spilled. The dura was not closed. The skull defect was repaired by a perforated tantalum implant measuring 5 x 6 inches, and the wound was closed. A rubber tissue drain was inserted through a stab wound, down to the tantalum implant. This drain was removed in a few days and replaced by daily aspiration of the cavity, followed by the injection of 50,000 units of penicillin. The wound healed readily but the patient's condition gradually failed and he expired on November 20, 1945, of intracranial sepsis due to Alcaligenes faecalis. Necropsy was not obtained. Examination of the specimen removed showed a chronic abscess in the tip of the temporal lobe and another in the posterior portion of the occipital lobe. There was no recurrence of the parietal lobe abscess.

Comment: The significant feature of this case is that at subsequent operations fifty-eight and eighty-four days after the original operation,

Case	Age	Sex	Date of Cranioplasty	Primary Focus	Method of Invasion	Location of Abscess	Bone Involvement	Surgical Procedure*
1	17	M.	6/27/44	Frontal sinusitis and osteomyelitis of frontal bone	Metastasis or by thrombophlebitis of sagittal sinus	Right parieto-occipital (multiple subcortical and subdural)	Previous osteomyelitis of frontal bone; none at operative site	Piecemeal excision of abscesses by electrosurgery; no drainage
2	33	F.	2/14/45	Acute right otitis media	Direct extension	Right temporal (subcortical)	Stalk adherent to dura over petrous bone	Complete excision of abscess; no drainage
3	6	M.	2/19/45	Acute right orbital abscess	Direct extension	Right frontal (subcortical)	Stalk adherent to dura over orbit roof	Complete excision of abscess; no drainage
4	17	M.	5/14/45	Acute frontal sinusitis and osteomyelitis	Direct extension	Left frontal (subcortical)	Frontal osteomyelitis and periosteal	Infected frontal bone excised; abscess drained through indwelling cannula
5	49	M.	5/15/45	Chronic mastoiditis left	Direct extension	Left temporal (subcortical and epidural)	Chronic mastoiditis; stalk adherent to dura over mastoid	Complete excision of abscess; postoperative irrigation through needles beneath scalp
6	15	M.	8/10/45	Chronic mastoiditis right	Direct extension	Right temporal (subcortical)	Chronic mastoiditis with cholesteatoma; stalk adherent to dura over petrous bone	Complete excision of abscess; no drainage
7	36	M.	8/8/45	Pneumonia	Metastasis	Right parietal (subcortical); temporal and occipital (subcortical—found at second operation)	None	Complete excision of abscess; no drainage
8	23	F.	10/19/45	Draining sinus in popliteal space—probably tuberculous	Metastasis	Left occipital (subcortical)	None	Complete excision

* In each case the cranial defect was closed by a perforated tantalum implant fashioned at the operating table and fastened to the outer table of the skull by means of 2 tantalum screws. The size of the implants varied from 6 x 6 cm. to 9 x 12 cm.

Pus Culture	Sulfonilimide Placed in Wound at Operation Grams	Postoperative Sulfadiazine Grams Daily	Placed in Wound at Operation Units	PENICILLIN Injected Into Operation Site Units	Intramuscular Units	Wound Healing	Result
Streptococcus anaerobius	None	None	10,000	10,000 every 4 hr. 12 times; then twice daily for 14 days; 10,000 intraspinally every 12 hr. 4 times	10,000 every 4 hr. for 16 days	Per primam	Alive and well 18 mo. postoperative
Diplococcus pneumoniae type I	5	4 for 16 days	25,000	20,000 every 12 hr. 4 times	15,000 every 3 hr. for 16 days	Per primam	Alive and well 11 mo. postoperative
Streptococcus salivarius	5	4 for 10 days	15,000	15,000 daily for 3 days	15,000 every 3 hr. for 10 days	Per primam	Death on 39th postoperative day from recurrent brain abscess; tantalum implant not involved
Alcaligenes faecalis and Streptococcus faecalis	5	4-6 for 27 days	None	Continuous irrigation of abscess cavity with 100/cc. saline solution for 4 days	15,000 every 3 hr. for 27 days	Per primam	Alive and well 8 mo. postoperative
Streptococcus anaerobius and Proteus vulgaris	5	4-6 for 41 days	10,000	Continuous irrigation of operation site with 100/cc. saline solution for 5 days	20,000 every 3 hr. for 34 days	Abscess formed about implant; drained 5-31-45; mastoidectomy 5-31-45; implant removed 6-15-45; drainage ceased 10-2-45	Alive and well 8 mo. postoperative
Bacillus coli and Staphylococcus albus	5	4 for 45 days	30,000	25,000 daily for 10 days	30,000 every 3 hr. for 25 days	Abscess formed about implant; drained 8-24-45; mastoidectomy 9-11-45; implant removed 9-19-45; drainage ceased 10-27-45	Alive and well 5 mo. postoperative
Streptococcus mitior	None	6 for 13 days	30,000	30,000 daily for 3 days	30,000 every 3 hr. for 16 days	Per primam	Death 3½ mo. postoperative due to other metastatic brain abscesses; implant was not involved
Sterile	5	4-6 for 9 days	20,000	None	30,000 every 3 hr. for 9 days	Per primam	Alive and well 3 mo. postoperative

the implant was found to be in good condition and free of infection. This occurred despite the fact that two previously undiscovered abscesses were still present in the brain.

Case 8—A colored woman, aged 23, was admitted to the hospital October 17, 1945, with a complaint of headache, loss of vision, and impairment of memory. The symptoms began four months previously, following childbirth. The only significant findings were a severe papilledema, a complete right homonymous hemianopsia, and a healed scar from a previous chronic draining sinus in the left popliteal space. The spinal fluid pressure was 530 mm. of water and it contained no cells. The clinical diagnosis was left occipital lobe tumor or perhaps tuberculoma.

October 19, 1945, a left occipital craniotomy was performed. The dura was thickened and adherent to the cortex near the sagittal sinus. Beneath the cortex a large firm nodular mass could be felt. A biopsy of the mass resulted in the discharge of 2 or 3 ounces of thick pus. The large abscess was then freed from the falx and removed by blunt dissection with the attached dura. The cavity was irrigated with saline, the bone flap discarded, and the bony defect covered with a perforated tantalum implant. The dura was not closed. One hundred thousand units of penicillin was given intravenously and 20,000 units was placed in the brain cavity. Five grams of sulfanilamide was placed on the outer surface of the implant, and the scalp was closed.

For nine days following operation the patient was given 30,000 units of penicillin intramuscularly every three hours and 1 Gm. of sulfadiazine orally four to six times daily. Convalescence was satisfactory, and she was discharged from the hospital October 30, 1945.

The microscopic diagnosis on the abscess wall was tuberculoma. Culture of the pus was sterile, and guinea pig inoculation of the pus was negative for tuberculosis. In view of the gross and microscopic appearance this is classified as a tuberculous abscess.

The patient was seen January 18, 1945. She appeared to be in excellent health. The scalp was well healed but slightly fluctuant over the site of the implant. Fluid aspirated from this area was clear and colorless. It contained 60 lymphocytes and total protein content was 192 mg. per cent. The culture was sterile.

Comment: Perhaps this case should not be included in a series of infected cases since the culture of the pus was sterile and guinea pig inoculations were negative. Microscopically the abscess wall had the typical appearance of a tuberculoma except that tubercle bacilli could not be identified in it. It appears possible that this wound will subsequently break down, but even though it does, the patient has certainly profited by the protection which the implant has afforded.*†

SUMMARY

Tantalum implants were used to close skull defects in 8 infected cases (7 brain abscesses and 1 acute osteomyelitis of the skull). Primary healing of the wound occurred in 6 of the 8 cases. The wounds became infected in 2 patients in whom the implant was contiguous to chronically

* As this article was going to press on Feb. 14, 1946, the injected guinea pig was found to be sick. At autopsy tuberculosis was disclosed.

† The author wishes to express appreciation to Mr. A. Reich of the Department of Bacteriology for help and suggestions in the study of these cases.

infected mastoid and draining ear canal. The implants in these 2 cases were removed four and six weeks later. These patients were benefited by the temporary presence of the implant.

Two of the patients died, one of a recurrence of the brain abscess and the other of metastatic abscesses in other parts of the brain. In neither case was the presence of the implant a factor in the unfavorable outcome.

The presence of tantalum did not delay healing, but rather the healing process was aided by splinting and immobilization of the wound which the implant provided. These results attest to the passivity of tantalum implants and justify the continued use of the material in such cases.

Seven cases of brain abscess were treated by a new method, namely radical excision of the abscess and closure of the skull defect by a tantalum implant and closure of the scalp without drainage. The patients were then treated with penicillin and sulfadiazine. The results in these few cases justify the continued use of the method.

The efficacy of present day antibiotics demands a re-evaluation of the surgical principle that foreign material should not be used to repair a bone defect in an infected wound.

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SULFADIAZINE ANURIA

Report of a Case

W. J. ENGEL, M.D.

Renal damage and anuria, in patients being treated with the sulfa drugs, may be the result of true toxic injury to the renal tubules or of urinary obstruction. The latter, in turn, may be intrarenal or ureteral. The case presented represents an example of the latter.

CASE REPORT

A 61-year-old man reported to Cleveland Clinic on January 2, 1946, complaining of a swelling in the neck. This was thought to be a branchial cleft tumor, probably carcinoma, and operation was performed on January 4. The tumor was found to be partially cystic, but the hard, infiltrated wall could not be entirely removed, so the wound was packed open. On January 6 a secondary closure was made, and the patient was put on sulfadiazine, 1 Gm. every four hours, as a prophylactic measure against infection.

On January 9 at 4 a.m. the patient complained of painful distress in the suprapubic region and was unable to void. The administration of prostigmine and other ordinary measures for inducing urination were ineffectual. Catheterization disclosed no urine in the bladder.

Urological consultation was requested. The man was in acute distress with pronounced suprapubic pain and vesical tenesmus. The bladder was not palpable. There was tenderness in the suprapubic region with slight tenderness in the costovertebral angles. With the history of anuria and pain, bilateral ureteral obstruction was suspected and immediate cystoscopy advised.

Cystoscopy was carried out under pentothal anesthesia. There was no urine in the bladder. Inspection revealed an acutely reddened and edematous mucosa with numerous white clusters of crystals lying on the floor of the bladder. Projecting from each ureteral orifice was a bulging white mass of crystals, more pronounced on the right than on the left side (figure). After some manipulation the masses were dislodged, and packed crystals were found to extend up the ureter for a distance of about 1 cm. When these were finally passed, urine was obtained through the ureteral catheters. These were taped in for indwelling catheter drainage and a minimum of 3000 cc. of intravenous fluids ordered for that afternoon and evening.

On the day of cystoscopy the blood sulfadiazine level was 3.5 mg. per cent, the urea was 36 mg. per cent, and the white blood count 9700 with 13.0 Gm. of hemoglobin.

During the succeeding twenty-four hours the patient secreted 1850 cc. of urine and the catheters were removed. Recovery was uneventful, with daily urinary output above normal for the following three days.

DISCUSSION

Cases of this type have been reported frequently in the literature, and doubtless many others have occurred. I encountered several almost identical cases during my service in the Navy, and all responded to prompt cystoscopy and ureteral catheterization with uneventful re-

covery. Anuria is not limited to the use of sulfadiazine but occurs also when sulfathiazole or sulfapyridine is administered.

The incidence of this complication would seem rather low when one considers the large number of patients treated with the sulfonamides. Finland, Strauss, and Peterson[1] reported only one case of anuria due to ureteral obstruction in 446 patients treated with sulfadiazine.

Obstruction by crystals should be suspected whenever a patient who is on sulfonamide therapy has oliguria or anuria, for typical ureteral colic is not always present. In most cases there will be antecedent hematuria, usually microscopic, and crystals may be found in the urine,

FIG. View of right ureteral orifice showing crystalline impaction.

though failure to find them by no means excludes the condition. Symptoms generally attributed to renal or ureteral colic often will be present with pain and costovertebral tenderness. I have seen vesical tenesmus, so predominant in the case here presented, in one other patient, and in such cases acute urinary retention is usually suspected. The tenesmus is due to trigonal irritation and generally indicates obstruction in the lowermost part of the ureter. However, in any patient who develops anuria while taking sulfonamides, should all signs and symptoms fail to establish the diagnosis, immediate cystoscopy and ureteral catheterization should be performed.

The mechanism by which these obstructing concretions of sulfonamides develop is not completely understood, though certain observations

appear pertinent. It is not directly related to dosage or blood sulfa level, for it has been reported with patients on small dosage and with relatively low blood levels. In our case the blood level was only 3.5 mg. per cent. In a fatal case of sulfathiazole anuria, Prien, Crabtree, and Frondel,[2] by means of the polarizing microscope, identified the crystals in the renal tubules as acetyl-sulfathiazole. It is generally accepted that these obstructing concretions consist largely of the acetyl crystals.

The factors which influence the deposition of these crystals and concretions are:

1. Concentration of the drug in the urine, depending upon
   a. volume of fluid passing through the kidneys,
   b. renal function,
   c. blood level and dosage,
   d. urinary stasis.
2. Degree of acetylization of drug.
3. The hydrogen ion concentration of the urine.
4. Temperature of urine.

The value of giving alkalis to increase the hydrogen ion concentration of the urine has been shown in several reports, and it has been demonstrated that the crystals are more soluble in an alkaline solution. Jensen and Fox[3] state that the solubility of sulfonamide crystals is minimal at 5.6 pH to 6.6 pH; it is doubled or tripled at 7.5 pH and increased tenfold at 8.0 pH. Schwartz and co-authors[4] studied the urine of patients on sulfathiazole and sulfadiazine with and without the administration of alkali. With sulfadiazine they reported crystals (graded 1 plus to 3 plus) in 25.3 per cent of patients not taking alkali and only 16.7 per cent when soda was given. The respective figures for sulfathiazole were 67.8 per cent and 35.7 per cent. Although the giving of alkalis may be of some value, in my opinion it cannot be relied upon to replace an adequate fluid intake and output. At least two of the patients I saw were taking sodium bicarbonate with the sulfonamides when the ureteral obstruction occurred.

An adequate fluid intake is the single most important preventive of this complication and a necessary corollary is an adequate urinary output, which should never fall below 1500 cc. daily and should be greater if possible. If the concentration in the urine is kept below the level of saturation at any given hydrogen ion concentration, there is little danger of crystalline deposits causing obstruction. Furthermore, it would appear

that the more rapid flow of fluid through the kidneys would reduce the possibility of stasis. It seems reasonable to believe that tubular impaction of crystals may follow in a retrograde manner after urinary stasis has been created by concretions obstructing the ureters or the collecting tubules. This same opinion has been expressed by Prien, Crabtree, and Frondel.[2] They report a case in which sections of the kidney under the polarizing microscope showed acetyl-sulfathiazole crystals in the papillary ducts in the renal papilla but none higher in the collecting or convoluted tubules. Two factors thus appear necessary for crystalline impaction, stasis and reabsorption of water in the convoluted tubules producing a supersaturated solution of a rather insoluble salt. Each of these factors may be controlled by an adequate fluid intake.

The treatment of this type of obstructive anuria, once recognized, is immediate cystoscopy and ureteral catheterization with lavage of the renal pelves. Even if only one ureter can be catheterized, that will suffice, providing a flow of urine is obtained. Failing in this, pyelostomy or nephrostomy is indicated. The time factor appears to be important, for of 5 cases reported by Smiley,[5] 3 seen within twenty-four hours of the onset of anuria were relieved by ureteral catheterization, while in 2 patients seen thirty-six and seventy-two hours after the onset of symtoms, ureteral catheters could not be passed. Nephrostomy was required in one, and the other finally recovered by forcing fluids and administration of alkalis. This latter patient must have passed his concretion spontaneously. Renal decapsulation has also been reported with success, but in the reported cases pyelostomy was also done.

It is evident that the drug must be discontinued and fluids forced by the intravenous or any other route. There is usually a temporary lag in urinary secretion, but by the end of twenty-four to forty-eight hours there is a polyuria. The ureteral catheters are left indwelling until restoration of urine secretion is assured. This usually occurs in twenty-four to forty-eight hours. To leave them in position too long is inadvisable, for crystals may then obstruct the lumen of the catheter.

This complication is preventable and need not occur if proper attention is paid to the urinary output. This should be accurately measured in all patients receiving sulfonamides, and if it falls below 1500 cc., parenteral fluids should be given in addition to fluids by mouth. Daily urinalyses should be done, for the presence of red blood cells or crystals indicates that fluids must be forced.

CONCLUSIONS

1. Anuria due to the administration of sulfonamides is an emergency demanding prompt cystoscopy and ureteral catheterization.

2. Obstructing concretions of sulfonamides can usually be relieved by ureteral catheterization and lavage of the renal pelves. If the obstruction cannot be passed, pyelostomy should be done without delay.

3. Adequate fluid intake and urinary output are the best safeguards against this complication.

4. Simultaneous administration of sodium bicarbonate when giving sulfonamides is desirable.

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SURGICAL TREATMENT OF INTRACTABLE PLANTAR WARTS

J. A. DICKSON, M.D.

The majority of plantar warts are successfully eradicated by conservative measures such as escharotic solutions, electro-desiccation, or irradiation in the form of x-ray. Comparable results are obtained by each of the above methods, 60 per cent to 90 per cent cures. Escharotics are reserved for simple cases, and electro-desiccation and irradiation are employed when local application of these substances fails. If a single method is desired, the selection would undoubtedly be x-ray, for this treatment is painless, short, successful, and safe, provided the treatment is administered with due respect to the tolerance dose.

It is recognized, however, that no matter how skillfully used, these methods fail in at least 10 per cent of cases. These intractable problems are not only distressing but often calamitous to the patient. After many years of therapy extremely painful ulceration on the plantar surface of the foot may still persist. This ulcer invariably extends through the deep fascia, and the dermatologist and roentgenologist feel thay have run the

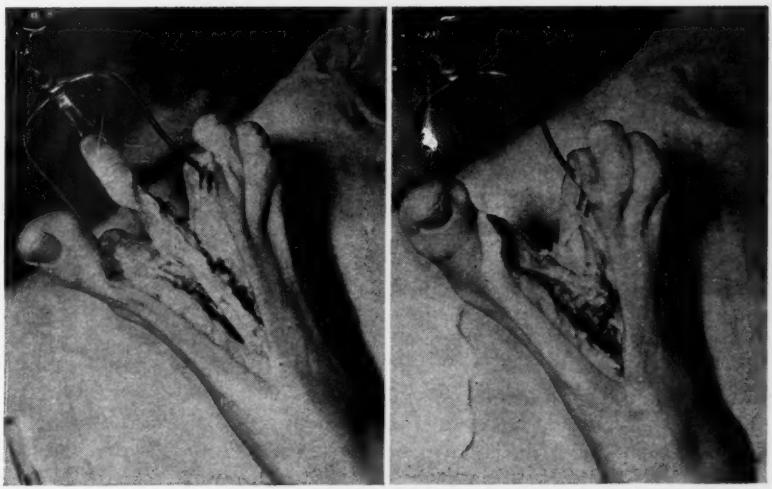

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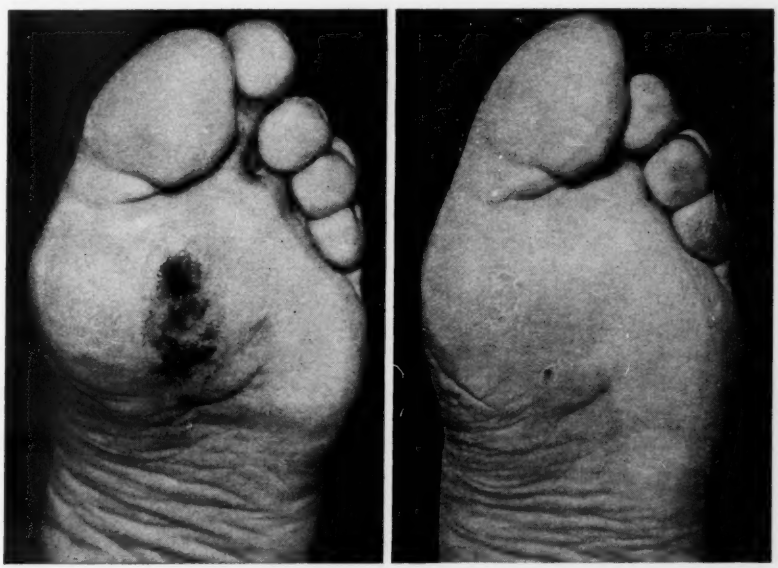
FIG. 1. Showing pie operation, (a) subperiosteal resection of the metatarsal bone, and (b) complete removal of metatarsal bone.



a *b*

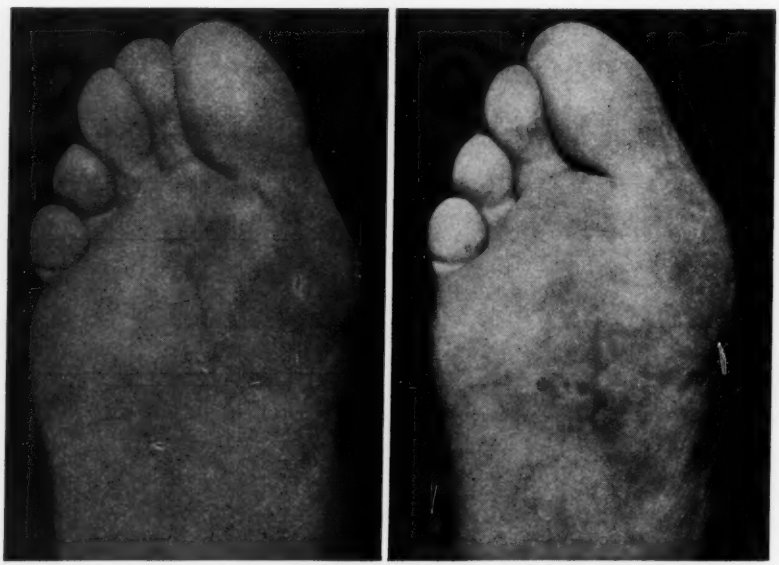
FIG. 2. Case 1. (a) Condition of foot before, and (b) after operation.

gamut and that further cautery, x-ray or radium treatment is contra-indicated.

For this type of plantar wart the only recourse is removal of the wart area in its entirety, and while this in itself presents no difficulty, the restoration of the operative site to a painless weight-bearing area involves many surgical problems. The amount of tissue removed may make immediate closure impossible, and even though approximation of the skin edges can be accomplished, it is performed under such tension that the resulting scar becomes thick, unyielding, and painful. Full thickness grafts, pedicle transplants from the involved foot or opposite calf, though successfully transferred, retain the characteristics of the donor site, and the thin skin does not furnish sufficient protection to weight-bearing.

In many instances, even though the defect could be sutured without undue tension, or a full thickness graft could be successfully transferred, the pressure of the overlying metatarsal head gradually transforms the operative scar and adjacent weight-bearing area into a dense, painful cicatrix as productive of symptoms as the original wart.

I thought that the removal of a V section of the foot, including a wide excision of the wart with a toe and the corresponding metatarsal bone,



a *b*

Fig. 3. Case 2. (a) Condition of foot before, and (b) after operation.

would bring about the desired effect. This operation would allow primary closure without tension and eliminate the use of grafted skin. Removal of the metatarsal bone would convert the operative site into a non-weight-bearing area, and healing without a painful scar would be accomplished.

At first it seemed heroic treatment to remove a section of the foot to cure a wart, but these intractable warts are serious problems and require radical treatment.

In 1940 a patient with a large warty ulceration on the plantar surface under the head of the second matatarsal bone, having sought relief for years, begged for an amputation of her foot so that she might walk again without constant pain. Amputation of a toe together with the adjoining metatarsal bone was a conservative procedure in comparison with her request. This afforded an opportunity to try this procedure which I felt had many factors to commend it.

A wedge, or so-called "pie" operation, was carried out (fig. 1), removing the wart in its entirety together with toe and metatarsal bone. Closure was readily accomplished, anchoring together the heads of the first and third metatarsal bones with chromic gut sutures. Such an excellent and satisfactory end result was obtained that I have performed the same operation many times with results so uniformly gratifying that I feel it is the treatment of choice in many of these troublesome conditions.

In this presentation I wish to show 2 cases of the series so treated. Both these cases had the papillomatous growths under the head of the second metatarsal.

Case 1—A woman, 40 years of age, had a large, ulcerated, painful area on the ball of her foot for years. She had had many types of treatment, including cautery, trimming, and x-ray. At the time of examination she had a draining sore which had been present for over a year. Further x-ray treatment was felt to be contraindicated. Figure 2 (a) shows condition of foot before and (b) after operation. No tendency to cicatricial formation is evident in the scar.

Case 2—A woman, 23 years of age, had been having treatment for a plantar wart for a six-year period. She had had 8 surgical removals in addition to x-ray therapy and radium. Figure 3 (a) shows condition of foot before and (b) after operation. The scar is soft and pliable.

SUMMARY

The loss of the toe and accompanying metatarsal bone did not appear to interfere in any way with the normal function of the foot. In both cases it will be noted that postoperatively there is a soft, pliable scar. The weight-bearing surface is much more satisfactory than when grafts were used to bridge the defect.

PARENTERAL FLUID THERAPY

(*A General Consideration*)

R. H. McDONALD, M.D.

Parenteral fluid administration has been definitely established in the past three decades as a major therapeutic measure in preserving life and lessening morbidity in a great variety of pathologic states. These conditions include patients in both the so-called medical and surgical categories who present a common background of dehydration, starvation and acid-base imbalance. The value of this form of therapy lies in the ability to administer necessary fluid, electrolytes, and nutrients to patients in whom the normal gastro-intestinal function is temporarily in abeyance or relatively unable to supply the organism with adequate amounts. Ordinarily, the procedure has been carried on for short periods ranging from a few hours to a few days, but cases have been recorded of practically complete parenteral nutrition over a period of several weeks. The routes most commonly used are the intravenous and subcutaneous, but under special conditions the intraperitoneal, intrathecal, and intramedullary routes have also been utilized. The intravenous route is by far the most practical of these since it is readily available, and its use offers a minimum of discomfort to the patient. Since the infused fluid becomes quickly diluted in the veins, it is possible to administer both hypertonic and isotonic solutions with a considerable range in hydrogen ion concentration both above and below the plasma level. Fluids used subcutaneously must be isotonic and adjusted to a normal hydrogen ion concentration of tissue fluid in order to prevent local tissue irritation and damage.

The aims of parenteral fluid therapy are multiple, but largely interrelated. An adequate water intake is a major consideration. The importance of water in the economy of the body becomes apparent when one considers that it forms approximately 70 per cent of the body weight. Water exists in the body in three compartments all to some extent intercommunicating—intracellular, interstitial, and vascular. The intracellular compartment is greatest in volume and constitutes 50 per cent of body weight. The interstitial constitutes 15 per cent while the blood plasma and lymph make up 5 per cent. Loss of fluid from the interstitial and vascular compartments, which together constitute the extracellular fluid, occurs at an earlier stage than intracellular fluid loss and may seriously impede peripheral circulation and lessen renal function with attendant disturbance of physiologic and chemical balance in

the body. Plasma volume must be maintained and replacement occurs at the expense first of the interstitial fluid. An adequate amount of water is also necessary for diaphoresis and efficient functioning of the heat control apparatus. In temporary disturbances incident to excessive loss of water or insufficient intake, simple water replacement may be all that is necessary. Water as such must not be given parenterally, but must contain electrolytes or other substances such as glucose in sufficient amount to make an isotonic or hypertonic solution. Electrolyte replacement assumes equal importance with fluid replacement and assures the maintenance of the necessary proper osmotic tension of body fluids. Sodium chloride is the primary salt used, but may be supplemented by salts of potassium, magnesium, and calcium in an attempt to imitate body chemistry as carefully as possible. Electrolyte imbalances incident to disease frequently alter the hydrogen ion concentration of body fluids either toward the acid or alkaline side. Clinical and laboratory recognition of such pathological imbalances is possible, and proper parenteral therapy should be given to aid in restoring the balance. Maintenance of the reaction of body fluid at pH 7.4 or close thereto is essential for proper metabolic processes. The caloric intake of the body may be maintained parenterally and all three of the major food factors may now be given in this manner. Carbohydrate usually represented by dextrose, protein by the amino acid mixtures produced by acid hydrolysis or enzymatic action on casein, and highly emulsified fat have been shown to be suitable for intravenous nutrition. The diet may be further supplemented by accessory food factors, all known vitamins, with the possible exception of the A-D group, having been successfully given parenterally. Plasma protein deficit may be counteracted by intravenous administration of plasma or serum or some fraction thereof, and anemia may be overcome by use of whole blood.

Clinically, the need for parenteral fluid therapy must be considered in every patient in whom there is a history of excessive weight loss or insufficient fluid intake over periods of more than a few hours, and in whom it is impossible to give adequate replacement by mouth. The indications include all lesions of the intestinal tract which are obstructive in nature and associated with excessive vomiting. In this connection, loss of fluid induced by use of the Wangensteen suction apparatus or Miller-Abbott tube must also be considered. In most of the clinical states described above, the tendency for alkalosis exists, due largely to the excessive loss of hydrochloric acid from the gastric secretion. Dehydration is, however, frequently accompanied by acidosis, partially because of the accompanying starvation and also because of deficient blood circulation with resultant anoxemia and impaired renal function

with attendant retention of acid metabolites. Diabetic coma is accompanied by dehydration and an acidotic tendency from ketosis. The vomiting of uremia is accompanied by dehydration and acidosis from loss of fixed base, retention of acid metabolites, and failure of the ammonia-forming renal function. Excessive loss of fluids from the bowel in diarrhea or from intestinal, biliary, or pancreatic fistulae is usually accompanied by acidosis due to excessive loss of base. An acidotic tendency is usually present also in loss of fluids in acute infections and in hemorrhage.

The necessity for fluid therapy is usually evident from simple observation of the patient. The skin is dry and harsh, the tongue is dry and coated, and the mucous membranes lack the normal glistening, moist appearance. The subcutaneous tissues lack their normal turgor. The peri-orbital tissues appear depressed and tension of the eyeball is reduced. The pulse rate is increased and the peripheral circulation appears feeble. Deep and exaggerated respirations suggest the possibility of an acidotic state, but may be seen also in stimulation of the respiratory center as from an encephalitis or tumor and are then usually associated with respiratory alkalosis. More shallow and irregular respirations suggest the probability of an alkalotic tendency if shock and emphysema can be excluded. Oliguria is certain to exist with dehydration, but the urinary hydrogen ion concentration cannot be used as an indication of acidosis or alkalosis, since it may be affected by urinary tract infection and does not necessarily reflect the chemical balance in the body. Thus, urinary infection may render the urine alkaline in acidosis, and in dehydration with alkalosis the urine may be acid if the base concentration of the plasma is below normal.

Generally, the dehydrated patient shows mental sluggishness and drowsiness. He may complain of headache, weakness, thirst, or abdominal pain. Cyanosis may develop and if dehydration is unrelieved, coma may supervene sometimes with convulsions. Tetanic manifestations with muscular hypertonicity, hyperactive reflexes, a positive Chvostek or Trousseau sign or carpopedal spasm are frequently seen as part of the alkalotic picture and are explained on a basis of reduction of available ionizable calcium associated with decreased hydrogen ion concentration.

Careful clinical records of fluid intake and the amount and manner of fluid loss constitute valuable data on which parenteral therapy may be reasonably based. In addition, they suggest the probability of disturbances of acid-base balance which may be associated with dehydration. The amount of fluid which may be lost is much more than is generally appreciated. The average adult male secretes in a twenty-four hour period 2500 cc. of gastric juice, bile 500 cc., pancreatic juice 700 cc., and 3000 cc. from the intestinal mucosa. If to this amount is added

saliva secretion of 1500 cc., a total twenty-four hour secretion of fluids of 8000 cc. from the gastro-intestinal tract is concerned which may in a large fraction fail to be normally reabsorbed. Some idea of the importance of this loss may be obtained by comparing this with the total plasma volume of 3500 cc. and a total extracellular fluid volume of 14,000 cc. It must be remembered that this gastro-intestinal fluid contains also the electrolytes of the extracellular fluid in different proportions, but at the same osmotic level. Excessive urinary output, as in diabetes mellitus and diabetes insipidus, must also be considered as well as excessive insensible fluid loss in perspiration and hyperpnoeic respiration. Serial determinations of body weight may offer some help in calculating the loss of fluid, since the greater proportion of weight loss in short periods must be in fluids, approximately one-half of which comes from the intracellular compartment.

The clinical appraisal of the patient should be supplemented by certain laboratory procedures which will be helpful in confirming the diagnosis and suggesting the proper line of therapy. The urine will usually be decidedly concentrated unless there has been pre-existing renal disease. Moderate amounts of albumin and a few casts may be present from toxic renal damage. Reductions of plasma volume may be evidenced by increased hemoglobin readings, increased red and white blood counts, and a rise in plasma protein concentration, but it must be remembered that these findings may be to some extent masked if there has been hemorrhage. A decrease in concentration of hemoglobin, blood counts and plasma protein will suggest the necessity for replacement with whole blood or plasma. Blood chloride estimations are of relatively little value, since the chloride ion level varies considerably with changes in acid-base balance. Total base levels give valuable information in regard to the fixed base of the extra-cellular fluid. Carbon dioxide combining power readings cannot be depended upon entirely without clinical correlative data to indicate either acidosis or alkalosis, although they are for the most part reliable where the acid-base imbalance is of metabolic origin. Where acid-base imbalance is of respiratory origin, significance of the findings is frequently reversed. Thus, in acidosis accompanying emphysema the carbon-dioxide combining power may be above normal and in alkalosis of primary hyperventilation it may well be beneath the average normal. The presence of acidosis or alkalosis may be definitely established by determining the serum hydrogen ion concentration, the outer limit compatible with life ranging from pH 7.0 to pH 7.8.

No specific rule of thumb is available for recognition of the degree of dehydration which exists in any particular patient and no mathe-

matical formula may be used to calculate the amount of parenteral fluid necessary. Some help may be obtained from recognition of the amount necessary for daily requirement to which must be added the sum total of fluid loss or the deficit which has accumulated in the period during which the dehydration occurred. The normal adult requires the production of 800 to 1000 cc. of urine in order to excrete the nitrogenous waste products of metabolism. If the renal function is poor, either from previous renal parenchymatous disease or from toxic interference with renal function as the result of disease, an obligatory polyuria may necessitate double the usual amount. Water loss in the stool normally averages 100 cc., but may be many times that figure in the presence of diarrhea. The insensible loss from the body averages 600 to 1000 cc., but may be often double that amount in fever with excessive perspiration and under high environmental temperatures. A normal 2000 cc. intake may be entirely inadequate therefore, especially in the presence of antecedent dehydration which may approximate 6000 to 8000 cc. in severe cases. Partial replacement may be possible in many of these patients orally, but in general the patient who requires fluid replacement most urgently is able to secure only a fraction of the necessary amount by this route. It must be remembered that normally a considerable amount of water is obtained from water content of food and a smaller fraction from water of oxidation of food. Normally these two replace the insensible water loss of the body.

The main point in hydrating the patient is to provide the sodium chloride in water which supplies replacement of the main structural disturbance in the extracellular fluid. Distilled water as such cannot, of course, be given and in fact would not be satisfactory since water is held in the body only as a solvent, the chief solute of extracellular fluid being sodium chloride. Isotonic saline solution is, therefore, used as the main material, but obviously only a fraction of the fluid can be given in this way, since every 1000 cc. of isotonic saline solution carries with it 8.5 Gm. of sodium chloride. The daily requirement is about 6 Gm., and unless a considerable deficit has preceded the fluid administration an excess of salt may occur in the body. If renal activity is insufficient to remove the excess salt, fluid retention occurs, and a urinary output relatively low in relation to intake follows. This might readily be interpreted as indicative of the necessity for more fluid. It is important to remember that replacement of extracellular fluid requires sodium chloride solution, but that fluid for increased urine output can best be supplied in the form of glucose solution. The glucose is metabolized and the water having no saline content is readily available for urine formation. The combination of isotonic glucose (5 per cent) and isotonic

saline (0.85 per cent) solutions, therefore, supplies material necessary for major replacement of extracellular fluid and for urinary function, and is in most cases an ideal one for initial therapy. Furthermore, the glucose solution provides a specific remedy for ketosis which accompanies starvation as well as diabetic acidosis. It has definite nutritive value also since glucose is readily available for metabolism and supplies approximately 4.5 calories per gram. Concentration of saline solution to 3 per cent may be given intravenously where there is an obvious need of larger quantities of chloride and where severe alkalosis exists, but administration of these higher concentrations requires careful observation, and they are not to be recommended in the average case. For clysis isotonic saline solution may be used or an isotonic solution of 2.5 per cent glucose in 0.45 per cent sodium chloride. In many instances of mild dehydration without serious disturbance of acid-base balance and without previous starvation, the use of such simple fluids for a day or two is all that is required to allow body processes to restore normal function. Simultaneously, all other smaller items of the chemical structure of extracellular fluid will be supplied by processes of metabolism, particularly if it is possible to use small oral feedings.

In case of disturbance of acid-base balance toward the alkaline side, the use of saline solution is all that is necessary since it adequately replaces the chloride ion deficit which is the main structural defect. Sodium chloride solution (isotonic) contains approximately one and one-half times more chloride ions than plasma and will, therefore, increase the plasma chloride at the expense of the elevated bicarbonate ion. The excess sodium ion must be excreted and this demands adequate renal function and output. Simultaneous administration of glucose solution supplies adequate water and improves renal function to allow such discriminatory power on the part of the kidneys. Simultaneous saline and glucose solution is, therefore, ideal for alkalosis. Even in acidosis adequate replacement of extracellular fluid and material for urinary formation may allow the body to adjust its chemical structure, but inasmuch as this may require several hours it is considered best to add bicarbonate ions directly in the presence of severe acidosis. Sodium bicarbonate solution, 5 per cent, may be used intravenously, but ordinarily its use is not advisable in view of the high alkalinity of the solution and the rapid change in the carbonic acid bicarbonate ratio. Hartmann's solution which essentially contains sodium lactate with sodium chloride may be used and combined with glucose solution. The lactic acid radical is oxidized after absorption and the bicarbonate ion is formed slowly. A simpler method of replacing bicarbonate deficiency is to use one-sixth molar sodium lactate solution, which is practically isotonic, combined

with saline in proportion ranging from 1:5 to 1:2 depending upon the severity of the acidosis.

Where gastro-intestinal disability is of long duration or where there has been previous starvation, the use of parenteral therapy to supply caloric needs of the body becomes important. Glucose has been available for parenteral nutrition over a considerable period of time and until recent times has been the only source of energy available by this route. To increase the caloric value the use of higher concentrations than the isotonic 5 per cent has been advocated. However, only 10 to 12 Gm. of glucose may be oxidized per hour by the average normal adult and larger quantities may cause glycosuria and polyuria which will have an adverse effect in an already dehydrated patient. It has been shown, however, that approximately 4 times that amount may be given for short periods without significant hyperglycemia or glycosuria, and thus the caloric intake from carbohydrate may be increased. An adequate carbohydrate intake results in a body protein-sparing effect and keeps the nitrogen requirement at a minimum.

In recent years it has been possible to administer sufficient amino acids intravenously to meet at least basic protein needs. Amino acid preparations produced by acid hydrolysis of casein with added tryptophan were first used and have been largely supplemented by enzymatic hydrolysates of casein and pancreatic tissue. These contain approximately 80 per cent of nitrogen as amino acids and 20 per cent as dipeptide. The solution is protein free, biuret negative, and nonantigenic. Its use has been curtailed by the fact that reactions occur quite frequently if it is not introduced slowly. These reactions are characterized by nausea, vomiting, fever, polyuria, and at times, local venous thrombosis. Urinary nitrogen increases simultaneously with these reactions to a greater degree than is seen when a corresponding amount of plasma is used. The amino acid solutions are usually added to 5 per cent glucose or isotonic saline for intravenous use. The amount of amino acid administered should depend upon estimated nitrogen loss which has been sustained together with the maintenance requirement, the latter being kept at a minimum by adequate glucose therapy. Daily nitrogen loss in the adult under resting conditions may approximate 6.4 Gm. (40 Gm. of protein), but considerably more may be required under febrile conditions and in severely ill patients. With present materials it is rather difficult to supply adequate parenteral nitrogen intake, but hope exists that a better product may help to achieve this result. Protein deficits may also be overcome more promptly by use of whole blood or plasma, and these latter materials are essential where the object of therapy is control of shock or maintenance of osmotic pressure of the blood.

Fat may also be supplied in emulsified form, and a few reports are available in the literature of its successful use. Its use would appear to be attended by considerable difficulty and has not become general. The importance of emulsified fat would seem to be chiefly for the caloric value of the material and as a possible vehicle for the parenteral administration of fat soluble vitamins.

As a rule, parenteral therapy is not carried on for a sufficient period of time for the development of a marked avitaminosis. A latent avitaminosis may have been induced by antecedent starvation, and, inasmuch as thiamine deficiency is known to develop within a few days, its use in dosage of 5 to 10 mgm. daily would appear rational. Other vitamin B radicals such as nicotinic acid are available for intravenous use, and, in fact, the whole vitamin B complex may be used. Vitamin C and K may also be added to the parenteral fluid on specific indication.

The history of blood loss frequently indicates the necessity for whole blood transfusion, but it is well to remember that the same necessity may arise from toxic destruction of blood in the course of disease. Usually, parenteral fluid therapy should include a whole blood transfusion of approximately 500 cc. for the average adult every four or five days. Plasma transfusion may be indicated by low plasma concentration, and in recent years fractionation of plasma has allowed the use of albumin alone in conditions where this factor shows specific reduction. In low plasma protein concentration associated with nephrotic states, the correction of plasma protein deficit by transfusion has been disappointing. This may be due partly to the necessity of replacing very large amounts of protein, but it is surmised that in these conditions the plasma protein level is controlled in some way at a low level by a renal mechanism.

It may be said, therefore, that complete parenteral therapy with each of the major food elements, chief electrolytes and necessary water to adjust extracellular fluid, and vitamin therapy is now feasible for limited periods of time. Its use, however, is attended with definite mechanical difficulties and involves considerable discomfort to the patient. In its present stage, parenteral therapy is nutritionally inadequate as far as intracellular ions are concerned so that oral feeding with simple foodstuffs should be started as soon as feasible.

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BETA RADIATION IN OPHTHALMOLOGY*

A. D. RUEDEMANN, M.D., and OTTO GLASSER, Ph.D.

For the past five years, beta radiation from radium has been used at Cleveland Clinic in treatment of corneal scars and lid lesions.

Beta rays had previously been advocated by Moore in treatment of tuberculosis of the eye.[1] Since tissue reaction in ocular tuberculosis is a low-grade, inflammatory process, we analyzed the use of beta radiation as a possible treatment of corneal scars and lid lesions in which a low-grade inflammation is also present.

Most patients with corneal scars are dismissed with the final statement that nothing further can be done. For patients whose vision is limited to light perception or moving shadows, an increase to recognition of large objects or those as high as 1/60 is extremely welcome. Slight improvement frequently marks the difference between complete dependency and self-sufficiency.

At present only two types of radiation, x-rays and gamma rays of radium, are used to any extent upon the eye. Both must be carefully handled to protect the lens and retina. They are successfully used in treatment of ocular conditions requiring deep penetration: carcinoma, sarcoma, and deep orbital pathologic processes.

Beta rays which we employ require an amount of radon in this form of therapy which is both considerable and expensive. Furthermore, such amounts of radon are not always easily obtainable.

Although beta rays as used in our treatments are of high intensity they are easily absorbed and penetrate only superficial layers of tissue; therefore it is safe to use them for lesions of the cornea and adjacent areas.

In preparing our beta ray applicator we seal radon in a small glass sphere (see illustration, R) approximately 4 mm. in diameter with a wall 0.1 mm. in thickness, which absorbs the alpha rays. This glass sphere is inserted into a thin metal capsule with open end (B2, B3). This capsule is then inserted into an open-ended brass holder (B1, B4), the wall of which is 2 mm. thick. Only a small glass window thus separates the tissue from the beta rays. Ninety-seven per cent of the emanating rays consist of beta rays: gamma rays make up the other 3 per cent, the alpha rays being absorbed in the glass. The handle (A) 35 cm. long, is held at one end with the open window at the other end of the holder placed against the area to be treated. Standard precautions are taken against undesirable radiation reaching the operator.

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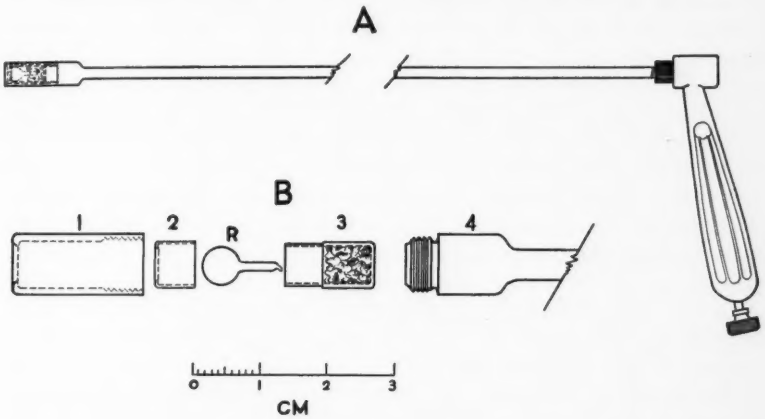
The gamma-ray strength of the radon bulb usually used is 200 millicuries. With this bulb the average dose applied is 5000 mg. Treatment time is therefore 5000/200 or 25 seconds.

Approximately fourteen to twenty-one days after treatment maximum reaction is observed. A four-week interval between treatments is advocated to permit the reaction to subside.

In treatment of palpebral conjunctival lesions, two-tongue blades are fastened end to end with a short overlap to hold the everted lid. A long applicator is used to raise the fold in the upper cul-de-sac.



In lesions of the ocular conjunctiva and the cornea, the surface is anesthetized with 0.5 per cent pontocaine and a speculum introduced before the beta radiation therapy. Patients are treated in a sitting position. A spotlight is used for illumination. A head loupe helps maintain proper corneal position, especially for minute corneal nebulae. Thus, no assistants are near the open end of the applicator. It is important that assistants avoid exposure to the rays, especially if many treatments are given. A lid speculum is necessary in treatment of corneal lesions because most patients cannot or will not hold their eyes still longer than five seconds, and immobility of the eye is necessary.

The first treatment was given in December, 1941, and treatments have been given every four weeks since that time, making a total of 725 treatments to over 100 patients, the average number of treatments being seven per patient.

Overgrowths of the lids are of minor importance from a visual aspect but of major importance from a cosmetic standpoint. Treatment of these

lesions by beta radiation has been satisfactory. The marginal areas have been left free without notching and without recurrences.

Beta rays have been used in the treatment of early tuberculosis by Gifford,[2] and we have used it in small basal cell epitheliomata in a total of 10 cases. This group with involvement of lashes and lid margin has long been neglected because we feared notching, and the patient feared operation. With beta rays only a few lashes are lost, and two treatments are usually sufficient. Incidentally, we have treated several basal cell epitheliomata of the face with equal success.

Lesions on the palpebral surface of the lid have also responded well to treatment. Vernal catarrh is treated by a variety of procedure. Treatment with beta radium was tried in a series of cases. After instillation of 0.5 per cent pontocaine, the field is freed of moisture and then held everted with a double-length tongue blade for the application. This procedure affords prompt relief. This condition, a polypoid degeneration of the membrane, requires more than one application in severe cases and, as in one case at Cleveland Clinic, may even require replacement of the membrane. In several lymphogenous overgrowths of the lid margin with involvement of one corneal margin, a satisfactory result was obtained. In all, about 15 patients were treated, and those who followed local and general therapy were definitely benefited. All have had complete investigation for allergic problems, and the general routine for their relief has been followed.

Under allergy treatment alone, follicles or polyps will not disappear even with a rigid routine. A change in the epithelium from large pavement blocks to a thin nonirritating membrane in which reversal cannot take place is the best that can be expected or anticipated.

Lymph overgrowths on the ocular conjunctiva usually disappear completely under beta radiation. We used radium needles with reasonable success in the past, but duration of treatment was much longer, and the results were not good when a lesion extended above the superior margin of the upper lid into the upper cul-de-sac.

Two patients with severe keratoconjunctivitis were given one application over the entire corneal area, and both responded well to therapy. After using beta radiation in treatment of a patient for severe conjunctivitis of obscure origin with the clinical appearance of an acute blennorrhea of the inclusion type, the beefy membrane and large follicles disappeared. This had been an old chronic condition with repeated exacerbations.

This report would be unduly prolonged if each case were described. Suffice it to say we have been impressed by the satisfactory results obtained in treating our allergic cases.

A similar group with ocular tuberculosis as that reported by Moore[1] gave comparable results. We have had a large number of these patients, and in all but two the lesions were on the cornea. Superficial scarring or superficial involvement, such as production of a nebula or at most a macula, gave the best results with almost complete disappearance of the scar or lesion. Treatment of corneal macula or corneal leukoma was moderately successful. Here again, general measures, such as heliotherapy, high vitamin intake, regulation of habits, and occupational therapy, were also used. In our experience, the cases treated with beta radiation had a shortened period of involvement and were followed by better results.

Corneal scrarring from various causes fell into three pathologic groups: corneal nebula, macula, or leukoma. The duration of the lesion played a part in the result of treatment. Depth of involvement was most important. Superficial lesions responded promptly and satisfactorily. With most corneal nebulae, the vision was definitely improved.

Maculae became less dense and smaller after beta radiation, and leukomas were improved by contraction of the area and thinning of the margins, although where there was little or no effect on the main lesion, gamma rays were used. The patient is benefited if the scar can be reduced, especially when it encroaches on the pupillary space.

Acute interstitial keratitis due to syphilis has shown improvement with beta radiation as an adjunct to systemic therapy. Four such cases have been treated. The earlier treatment is instituted, the better the result. Keratitis due to vitamin deficiency or trauma is also benefited.

Many patients have been treated for symblepharon, pseudopterygium, and recurring pterygium. These conditions present similar corneal problems: superficial overgrowth, deep infiltration, and frequently presence of a deep blood supply, which is marginal in origin but passes through the deep substantia propia. Treatment is directed to closure of the deep vascularization. This cannot be accomplished by surgery alone, but surgery with radium therapy approximately one week later has produced good results.

Several complete keratoplasties supplemented by beta radiation treatment were attempted with questionable success. We believe it is possible to enlarge a clear zone in the cornea, but we do not believe new corneal tissue can be produced. This is true of most corneal transplants. If the entire cornea is scarred, the transplant will not remain clear. Beta radiation, however, may help to maintain clarity in some patients.

We have also treated intractable blepharitis marginalis, distichiasis, herpes, and postsurgical scarring with varying results, mostly encouraging.

CONCLUSION

1. Beta radiation proved beneficial to many patients, because even slight improvement lessened their dependency and enhanced their usefulness.

2. Beta radiation offers another method in the treatment of corneal scars and certain lid lesions, especially if applied early and in conjunction with other therapy. We believe that gamma radiation of the most dense scars can be used in conjunction with beta radiation treatment.

3. Cost, lack of availability, and persistency of the scar detract from the value of beta radiation.

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TREATMENT OF CARCINOMA OF THE PROSTATE

CHARLES C. HIGGINS, M.D.

With the introduction of estrogen therapy and orchiectomy as supplemental measures in the treatment of cancer of the prostate, new concepts were made available for combating this disease.

Sufficient time has now elapsed to warrant evaluation of the various types of treatment. Opinions of other surgeons and a personal experience with 100 cases forms the basis for such an evaluation.

In 1941 Huggins demonstrated the effect of certain hormones upon carcinoma of the prostate.[1] With the advent of this knowledge a new era in the treatment of this disease has been entered.

Various treatments have been recommended: orchiectomy, administration of estrogen substances, and irradiation of the testes. Interesting observations have been made regarding such treatment. Alleviation of pain, pronounced regression of the primary neoplasm, and disappearance of metastasis have occurred in many patients. Some, however, do not respond to treatment satisfactorily; relief of symptoms is transitory, and in a few little benefit is obtained.

Randall in 1942 reported a series of 5 cases in which castration had been performed for carcinoma of the prostate in 1934.[2] Transurethral

resection was employed to relieve the obstructive symptoms. He stated that the clinical course following surgical castration was similar to that following a transurethral resection alone. This first suggested that the beneficial effects obtained by hormonal therapy would not exert a permanent effect.

A review of the cases of prostatic carcinoma occurring in two successive years is presented to evaluate the various types of treatment employed at the present time, their indications, and the end results.

In considering the role of radical perineal prostatectomy certain features warrant elucidation. Carcinoma of the prostate in 75 per cent of cases arises in the posterior lobe. It invades the remainder of the gland slowly; extension through the capsule is impeded by the two layers of Denonvilliers' fascia, which is devoid of lymphatics. During this time the disease is confined to the gland, although later the seminal vesicles are invaded or dissemination through the perineural lymphatics occurs. While the disease is confined to the prostate gland, radical perineal prostatectomy should be followed by a cure.

It has been my experience, however, that, due to the absence of symptoms, patients rarely present themselves for examination until the carcinoma has extended beyond the confines of the gland. The periprostatic tissue has been invaded as evidenced by fixation of the gland, or the lesion has extended beyond the base of the seminal vesicles, or has involved the membranous urethra. If radical operation is to be recommended, early recognition of the lesion is essential. Therefore, in patients in whom the lesion is still confined to the gland, metastases are not demonstrable, and phosphatase studies suggest the absence of metastasis, I believe a radical perineal prostatectomy should be recommended. Only one patient in the group was in this category. He lived for two years after operation when metastasis resulted in death.

HORMONAL TREATMENT

Three methods of approach are available in hormonal treatment of carcinoma of the prostate: (1) administration of estrogenic hormones, (2) surgical castration, and (3) irradiation of the testes. Surgeons, among them Kearns and Dean, prefer the administration of estrogens. Kearns states,[3] "Simple estrogen therapy will gain in favor because all the attainable benefits of castration minus some of the undesirable side effects are obtainable by the judicious use of the true hormone estradiol given to each individual by the most effective route."

Dean also has indicated a preference for the use of stilbestrol:[4] "When they first began to treat cancer of the prostate by modification

of the endocrines, alternate patients were treated by castration and by the administration of stilbestrol. After observing the results, 1 mg. of stilbestrol daily by mouth at bedtime has remained the primary treatment of choice."

I have arrived at similar conclusions after comparing the results secured by orchiectomy and estrogenic treatment and recommend stilbestrol 1 to 3 mg. by mouth daily.

By selecting cases occurring in two successive years, I hope to demonstrate the progressive decrease in the choice of orchiectomy in the treatment of carcinoma of the prostate and its replacement by estrogenic therapy. From Nov. 1, 1942, to Nov. 1, 1943, I treated 52 patients with carcinoma of the prostate. A bilateral orchiectomy was performed on 25 patients and estrogen therapy was the treatment employed for the remainder. From Nov. 1, 1943, to Nov. 1, 1944, of 49 patients with carcinoma of the prostate treated, 17 were subjected to bilateral orchiectomy. During 1945, however, the administration of estrogens practically replaced surgical castration as the treatment of choice.

In those patients treated by orchiectomy all androgenic activity of the body does not cease. Other androgenic activity is present after bilateral orchiectomy as indicated by excretion of androgens in the urine and presence of androgens in the adrenal cortex. Estrogen therapy, on the other hand, depresses the anterior pituitary gland and may depress the andromimetic function of the adrenal glands.

In 44 per cent of patients a decrease in the size of the primary neoplasm occurred following the administration of estrogens. The gland became softer in consistency and in a few instances it would have been difficult at a later date to arrive at a diagnosis of carcinoma of the prostate by rectal examination. Other surgeons still prefer bilateral orchiectomy for the relief of patients with carcinoma of the prostate. Scott,[5] for example, in 1945 reported 82 consecutive patients in various stages of development of the disease, all of whom were treated by orchiectomy. Emmett believes that,[6] "The indication for bilateral orchiectomy is carcinoma of the prostate with metastasis." He states further that his present practice is to advise orchiectomy primarily for patients suffering metastases for the relief of metastatic symptoms. In 61 per cent of the cases from Nov. 1942, to Nov., 1944, treated by orchiectomy a regression of the neoplasm occurred, with a softer consistency of the gland, and less fixation.

As stated previously administration of estrogens has practically replaced surgical castration during the past year. The only patients being subjected to bilateral orchiectomy are those bed-ridden from intolerable

pain and in whom I believed a more rapid response to treatment could be secured by castration.

IRRADIATION OF THE TESTES

Munger has advised irradiation of the testes to replace surgical castration.[7] In his hands this treatment compares favorably with the results secured by bilateral orchiectomy. This procedure has not been employed in any of the patients in this series.

The study of the acid and alkaline phosphatases is of considerable value in the diagnosis of metastases before bilateral orchiectomy or the administration of estrogens. It will be observed that following bilateral orchiectomy the acid phosphatase quickly approximates normal levels. In patients in whom metastasis to the bony skeleton had occurred it was observed that following castration there was an initial elevation of the alkaline phosphatase in 58 per cent of the cases. However, this was followed later by a decrease in the alkaline phosphatase. On the other hand, when estrogen therapy was employed there was a more gradual decrease in the acid phosphatase to normal limits. If metastasis were present the initial rise in the alkaline phosphatase was not so constant. If an elevation of the alkaline phosphatase occurred the later fall was more gradual.

According to Kearns,[3] deviation of the blood sedimentation rate occurs in 100 per cent of the patients and is an excellent procedure to follow the clinical progress of the patient. Remarkable improvement in the sedimentation almost invariably follows the institution of endocrine therapy. While I have not adopted estimation of the sedimentation rate as a routine procedure, but have relied on the acid and the alkaline phosphatase determinations, in a few cases in which such studies have been made I believe Kearns' opinion to be justified.

GENERAL CONSIDERATIONS

Castration or the administration of estrogens in a small group of patients treated by either method showed little response to treatment. The course of the disease is not arrested and death ensues. The second and largest group shows a definite and satisfactory response with pronounced improvement following either castration or the administration of estrogens. Following castration the pain due to metastatic involvement of bones disappears quite promptly in twelve to thirty-six hours, while from administration of estrogens similar relief occurs in seven to ten days. A patient who has been confined to bed with pain becomes active. Not only the pain disappears, but appetite and the general condition

also are noticeably improved. The patient gains in weight, probably due more to the eunuch state than to improvement in the general physical condition. In spite of this improvement it has been disappointing to find that after a period of eight to eleven months a relapse occurred in 58.5 per cent of the patients.

In the third group treated by orchiectomy or estrogen therapy a patient may continue in excellent health, free from symptoms for an indefinite period of time. Such a favorable course may occur in patients who have had no treatment at all. A patient, not included in this series, was diagnosed clinically several years ago as having carcinoma of the prostate. There was complete absence of symptoms and no treatment was instituted. He has been followed for fifteen years and has continued to be free of symptoms. Unfortunately this diagnosis was not confirmed by biopsy.

Another group of patients with carcinoma of the prostate requires relief of obstructive symptoms. Between Nov. 1, 1942, and Nov. 1, 1943, among 52 patients treated for carcinoma of the prostate, I performed a transurethral resection of the prostate on 17 to relieve obstructive symptoms. In the following year, 21 among the 49 patients were similarly relieved.

In the series reviewed there has not been a single instance of the complete disappearance of a metastatic lesion in the bones or the lungs following either castration or the administration of estrogens. It is true that in many instances roentgenograms led me to infer a definite improvement has occurred, but biopsy studies were not available to substantiate the impression.

Dean does not depend entirely upon the roentgenograms and states,[4] "We have experienced difficulty in recognizing x-ray evidence of changes in the bony metastasis during and after treatment." He relies on phosphatase studies to indicate the status of the bone lesions.

In reviewing the results obtained in treatment of carcinoma of the prostate either by castration or estrogen therapy it is essential to compare these results with a similar group of patients in whom such therapy was not employed.

Bumpus,[8] in a review of 1000 cases of carcinoma of the prostate, reported that 485 patients who received no treatment from the onset of symptoms lived for an average of thirty-one months. Among these untreated patients 66.7 per cent had untreated metastasis at the time of diagnosis, and died within nine months.

As previously mentioned 58.5 per cent in this series had a recurrence of symptoms nine to eleven months after orchiectomy or estrogen therapy. The disease continued to progress in spite of all therapeutic pro-

cedures. It has been my experience that the administration of estrogens helps but little when the patient has had a recurrence after castration. There appears to be no significant difference between the results of estrogen therapy and those of orchiectomy. In our series of cases of carcinoma of the prostate treated by orchiectomy or estrogens 38 per cent died within twelve to fourteen months.

32.6 per cent of patients treated by orchiectomy succumbed within twenty-four to thirty-two months; dead or delayed failures in same period of time 56.4 per cent; 62 per cent succumbed in a like period of time when treated with estrogens, and 68.9 per cent are dead or delayed failures. All were clinically free of metastasis at the time treatment was instituted. When metastasis was present at the time of treatment, 71 per cent died in a similar period of time.

An important question now arises: If orchiectomy or estrogen therapy is to be employed for carcinoma of the prostate, and the relief of symptoms is only temporary, should it be recommended as soon as the diagnosis is established or held in reserve until urgently required? Treatment at the later time may be expected to afford relief from pressure, from local invasion of the growth or of a metastasis. Another variation occurs between the orchiectomy group and the stilbestrol group in that in the latter group several patients discontinued stilbestrol medication. In many advanced cases stilbestrol was also used as a palliative procedure.

Bugbee believes,[9] "If orchiectomy is carried out early in the disease, the relief it affords at a later period when it is most needed, is denied the patient." Nesbit and Cummings likewise comment[10] that "the maximum benefit to the patients may be derived by delaying endocrine treatment until indicated by advanced or metastatic lesions."

In view of available statistics demonstrating the temporary relief afforded by castration or estrogen therapy, the question arises whether in the majority of cases endocrine therapy should be reserved for later relief of pain associated with this disease.

SUMMARY

1. Orchiectomy or estrogen therapy is not a cure for carcinoma of the prostate.

2. Estrogenic therapy or orchiectomy have about the same value in treatment.

3. Obstructive symptoms may be relieved by transurethral resection of the obstructing gland.

4. Radical perineal prostatectomy should be recommended when it is technically possible and when the disease is contained wholly within the gland.

5. Because of the temporary relief it affords it may be wiser to reserve the employment of endocrine therapy until the disease is well advanced.

6. Acid and alkaline phosphatase studies are a valuable aid in the diagnosis of prostatic cancer before and after operation.

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CLEVELAND CLINIC BUILDINGS

Fronting on East Ninety-third Street

a. Seven stories to be added to the Clinic in 1946

b. Research Division

c. Additional building for 35 hospital beds in rear of this entrance

d. Cleveland Clinic Hospital

e. Hospital addition for 120 patients